Dengue

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

UNCLASSIFIED

Acknowledgments

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MAY 2015

Disclaimer

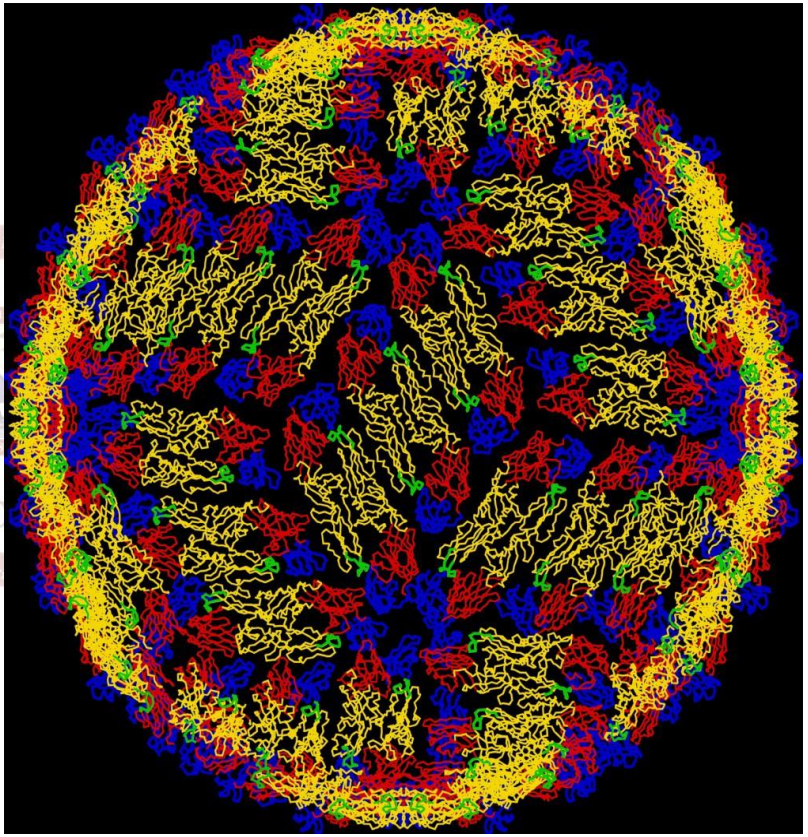
The views expressed in this presentation are those of the speaker and authors, and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government

Lecture Objectives

1. Understand the **global distribution** of dengue virus circulation and disease.
2. Appreciate the spectrum of **dengue clinical phenotypes** and recognize severe forms of the disease.
3. Understand the nuances of **treating dengue** and best management practices.
4. Become familiar with **countermeasure development** efforts.

Lecture Outline

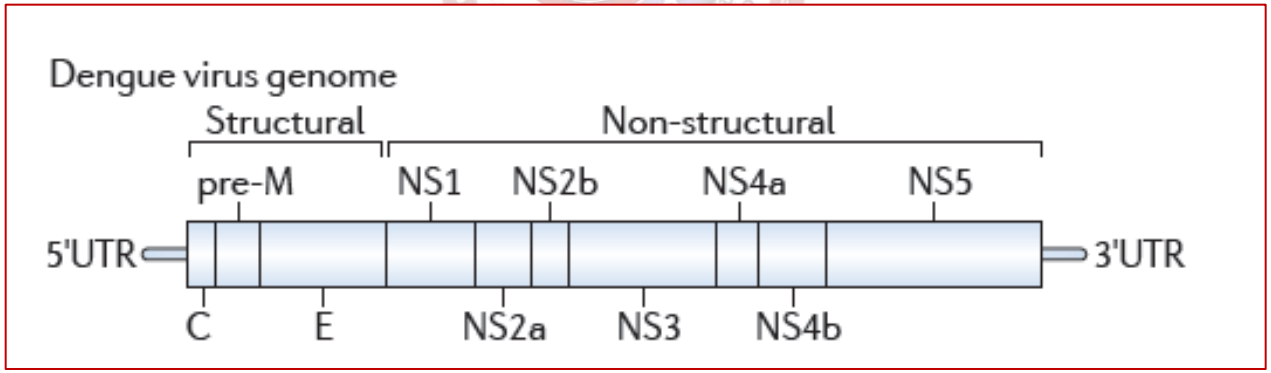
- Introduction
- Epidemiology
- Clinical Phenotypes
- Pathophysiology
- Diagnostics
- Management
- Vaccine Development



Kuhn, R., Purdue University

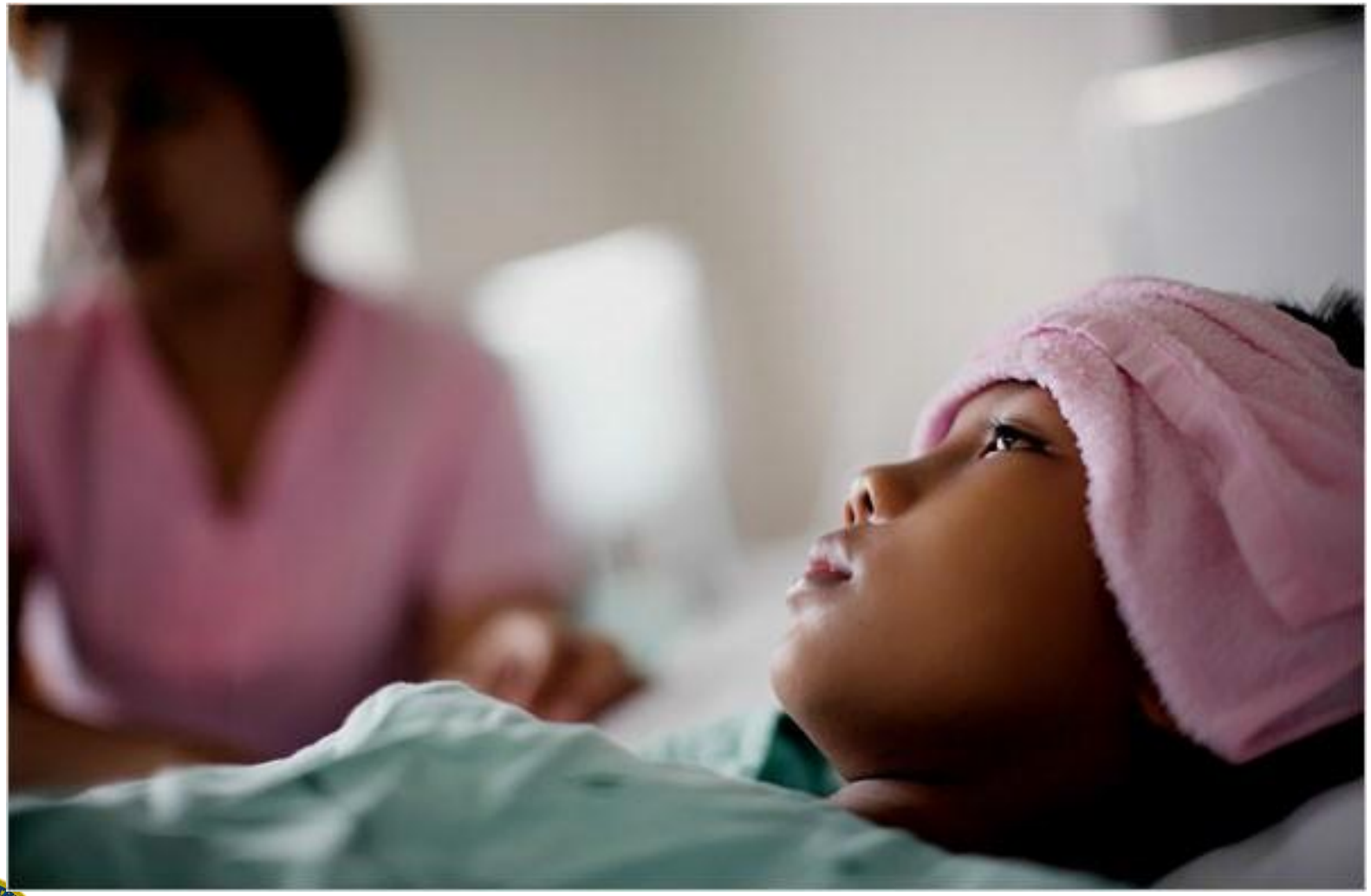
Dengue

- Basics
  - Family Flaviviridae, Genus Flavivirus, Species Dengue
    - Same family as WNV, YF, JE, Zika
  - RNA virus, 3 structural and 7 non-structural genes
    - Different functions during infection process
    - Different targets for drugs/vaccines



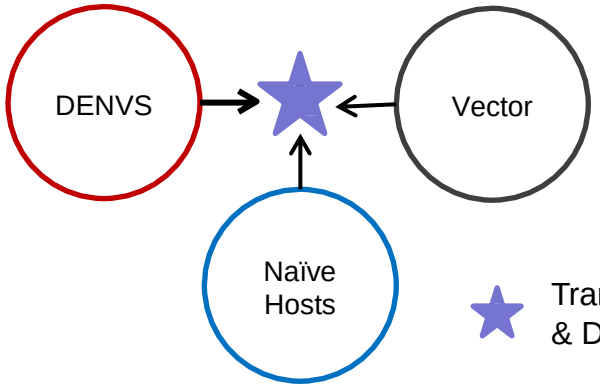
  - 4 dengue virus types: DENV-1-4
    - Multiple genotypes within each dengue virus type

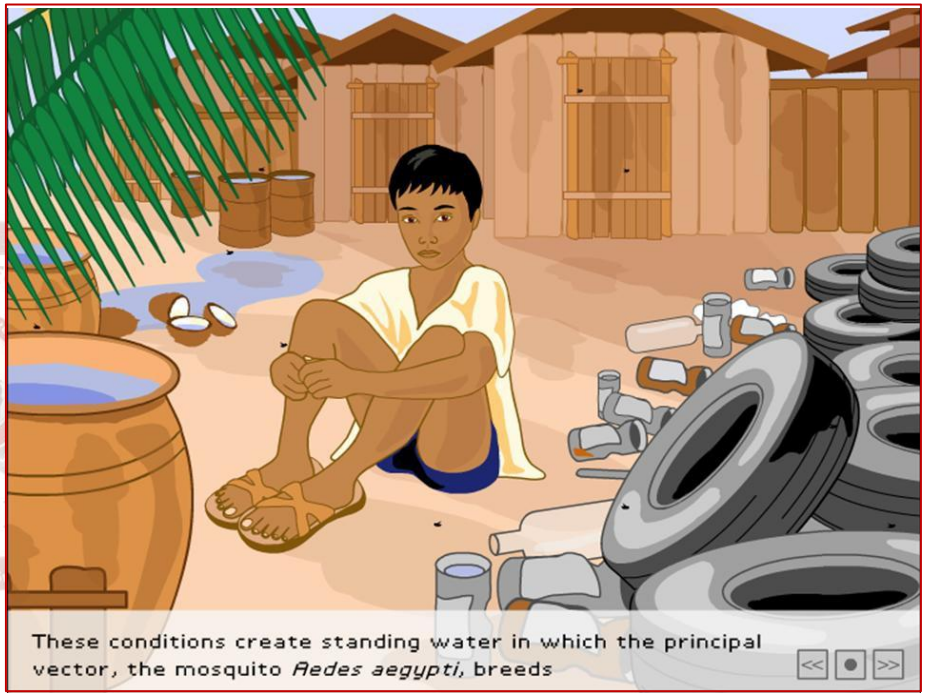
Dengue Epidemiology



Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)

Factors Driving Transmission





- Dengue viruses
  - Human travel
  - Viral evolution
- Naïve hosts
  - Population growth
  - Increased urbanization
- Vector
  - Ecologic changes
  - Evolution

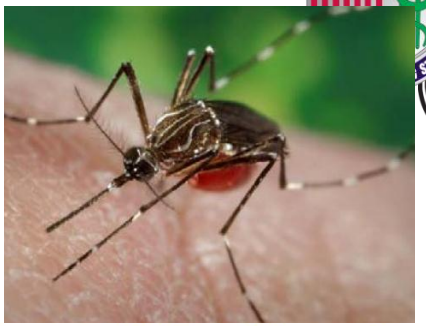
Mosquito Vectors

- *Aedes* mosquitos
  - Female bite, day time biter
  - Mosquito incubation period of 8-12 days and remains infective
  - Urban area, breed in or by houses
  - Man made or natural water containers
  - Short flyers

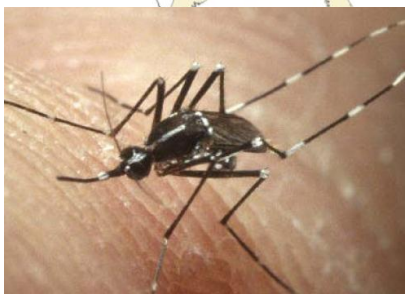
- *Aedes aegypti*
  - Principal vector
  - Multiple blood meals
  - Tropical and subtropical distribution

- *Aedes albopictus*
  - Less efficient vector
  - Wider distribution, better cold tolerance
  - Locally acquired cases in non endemic count (Japan in 2014)

CDC



Approximate distribution of *Aedes aegypti* in the United States*



Approximate distribution of *Aedes albopictus* in the United States*

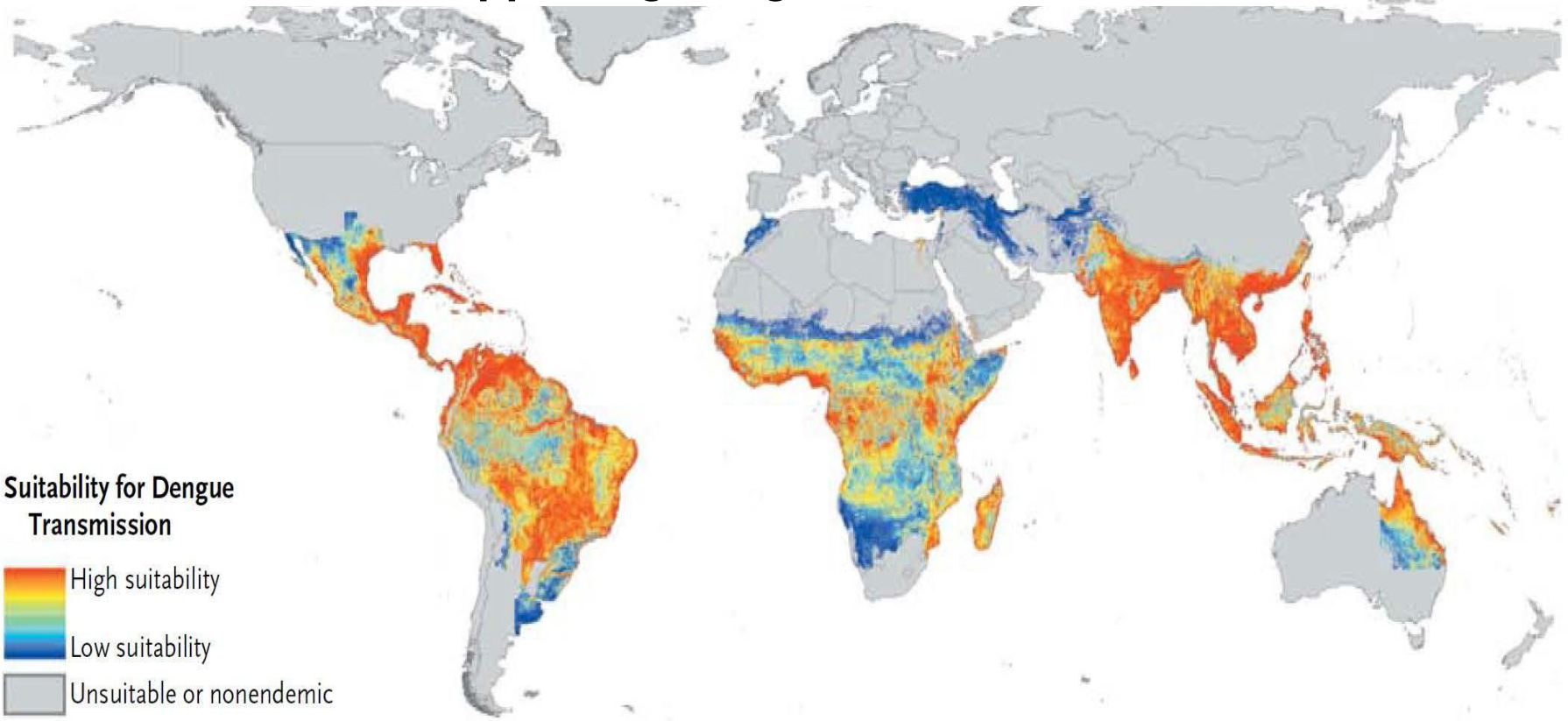
CURRENT CONCEPTS

Dengue

Cameron P. Simmons, Ph.D., Jeremy J. Farrar, M.D., Ph.D.,
Nguyen van Vinh Chau, M.D., Ph.D., and Bridget Wills, M.D., D.M.

N Engl J Med 2012;366:1423-32.

Areas supporting dengue virus transmission.



Is dengue a threat to the blood supply?

D. Teo,*[1] L. C. Ng†[1] & S. Lam* *Blood Services Group, Health Sciences Authority, and †Environmental Health Institute, National Environment Agency, Singapore

Transfusion Medicine, 2009, **19**, 66–77

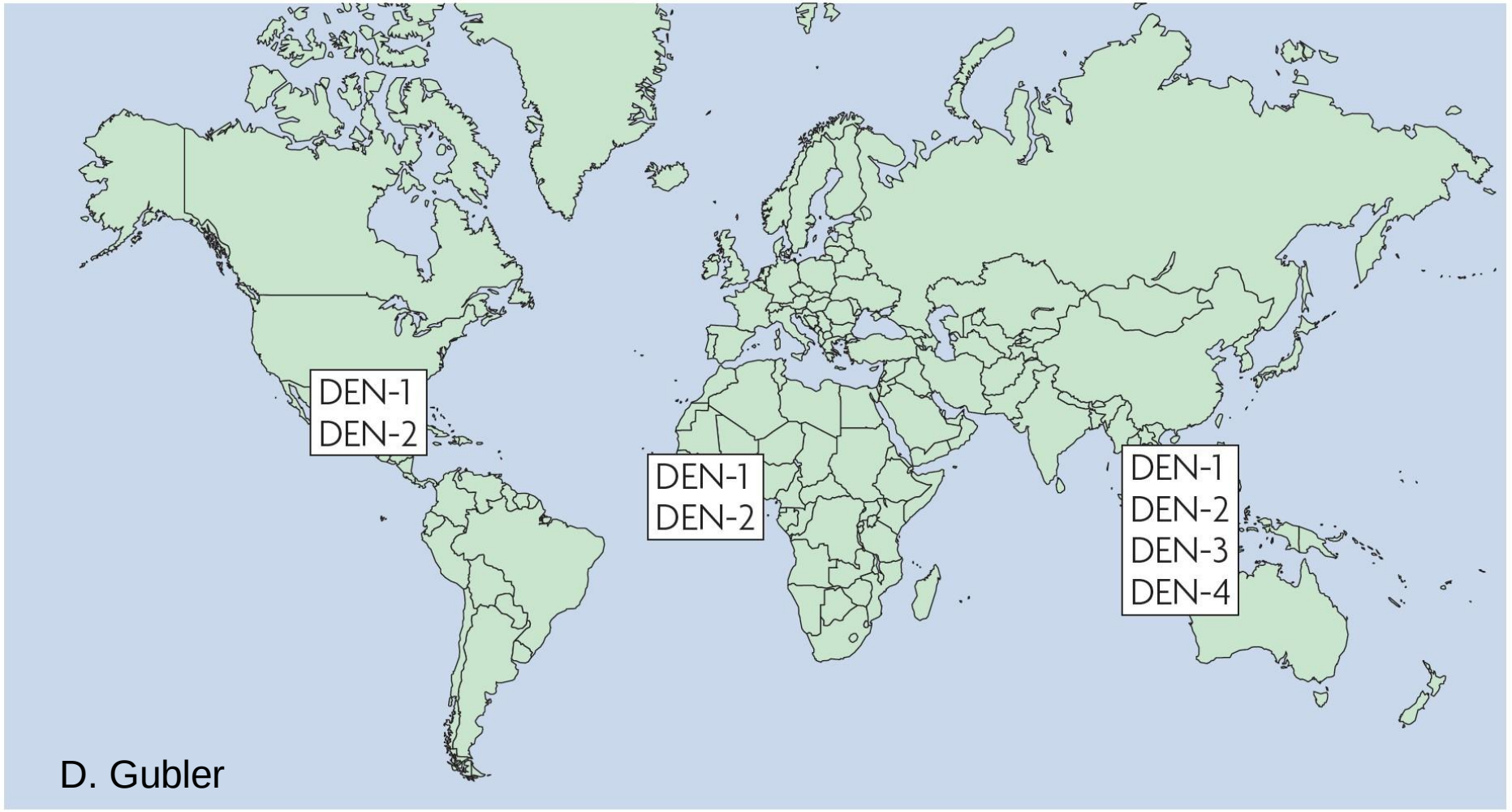
- Laboratory acquired?
- Blood supply?
- Organ donation?

Table 3. Dengue and donor deferral

Country	Donor deferral measures for dengue
Singapore*	6 months deferral for history of dengue infection 3 weeks deferral for history of fever No travel-related deferral for dengue
Hong Kong*	6 months deferral for history of dengue infection 2 weeks deferral for history of fever No travel-related deferral for dengue
Sri Lanka*	No specific deferral for history of dengue infection 2 weeks deferral for history of fever No travel-related deferral for dengue
Australia†	4 weeks deferral for history of dengue infection No travel-related deferral for dengue
New Zealand‡	4 weeks deferral for history of dengue infection No travel-related deferral for dengue
UK‡	2 weeks deferral for history of dengue infection No travel-related deferral for dengue
United States‡	4 weeks deferral for history of dengue infection No travel-related deferral for dengue

*Endemic for dengue.
†Non-endemic except parts of Northern Australia.
‡Non-endemic.

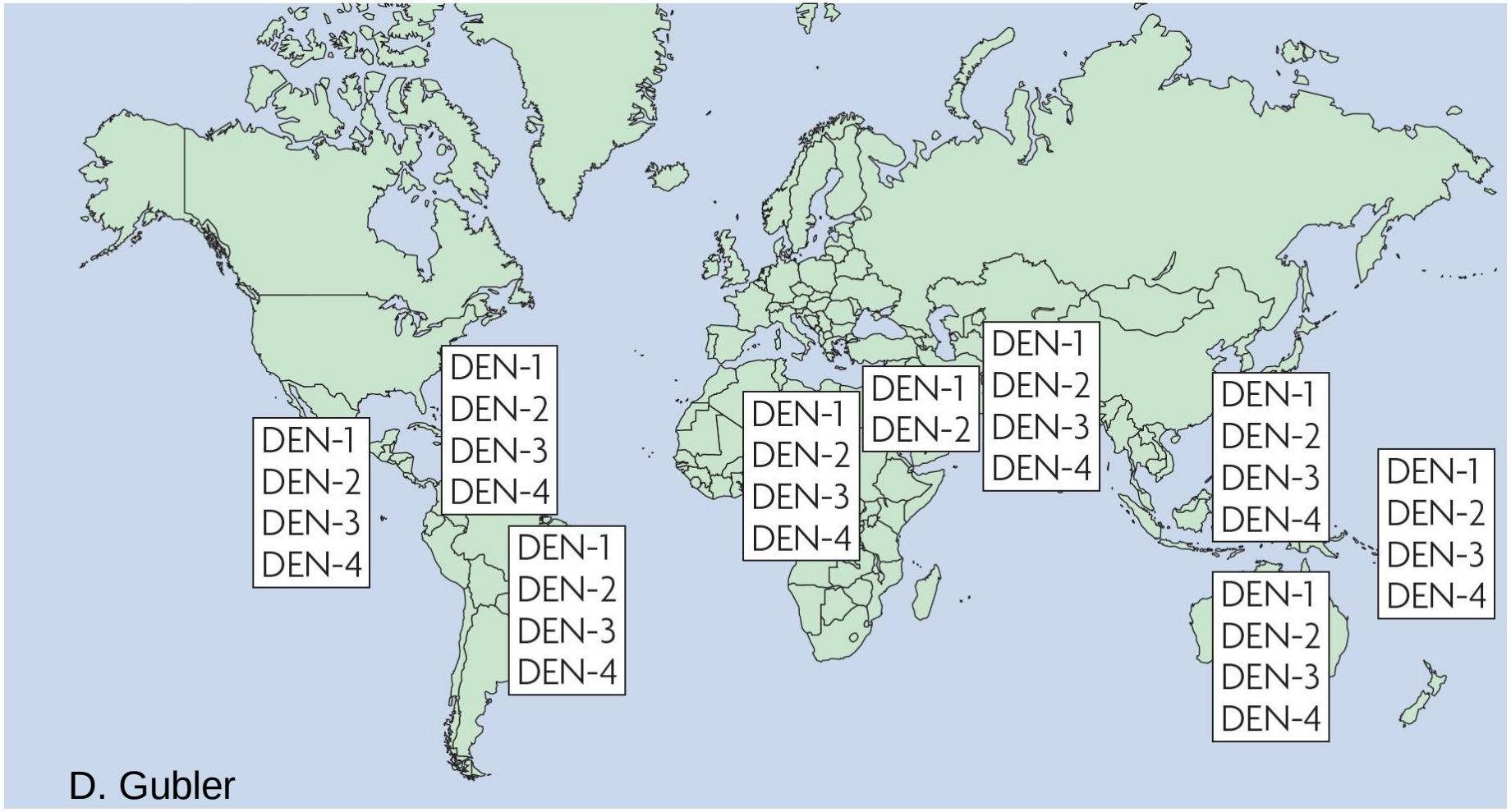
DENV Type Distribution - 1970



Global Air Travel Flight Plans

http://upload.wikimedia.org/wikipedia/commons/a/ac/World-airline-routemap-2009.png

DENV Type Distribution - 2004



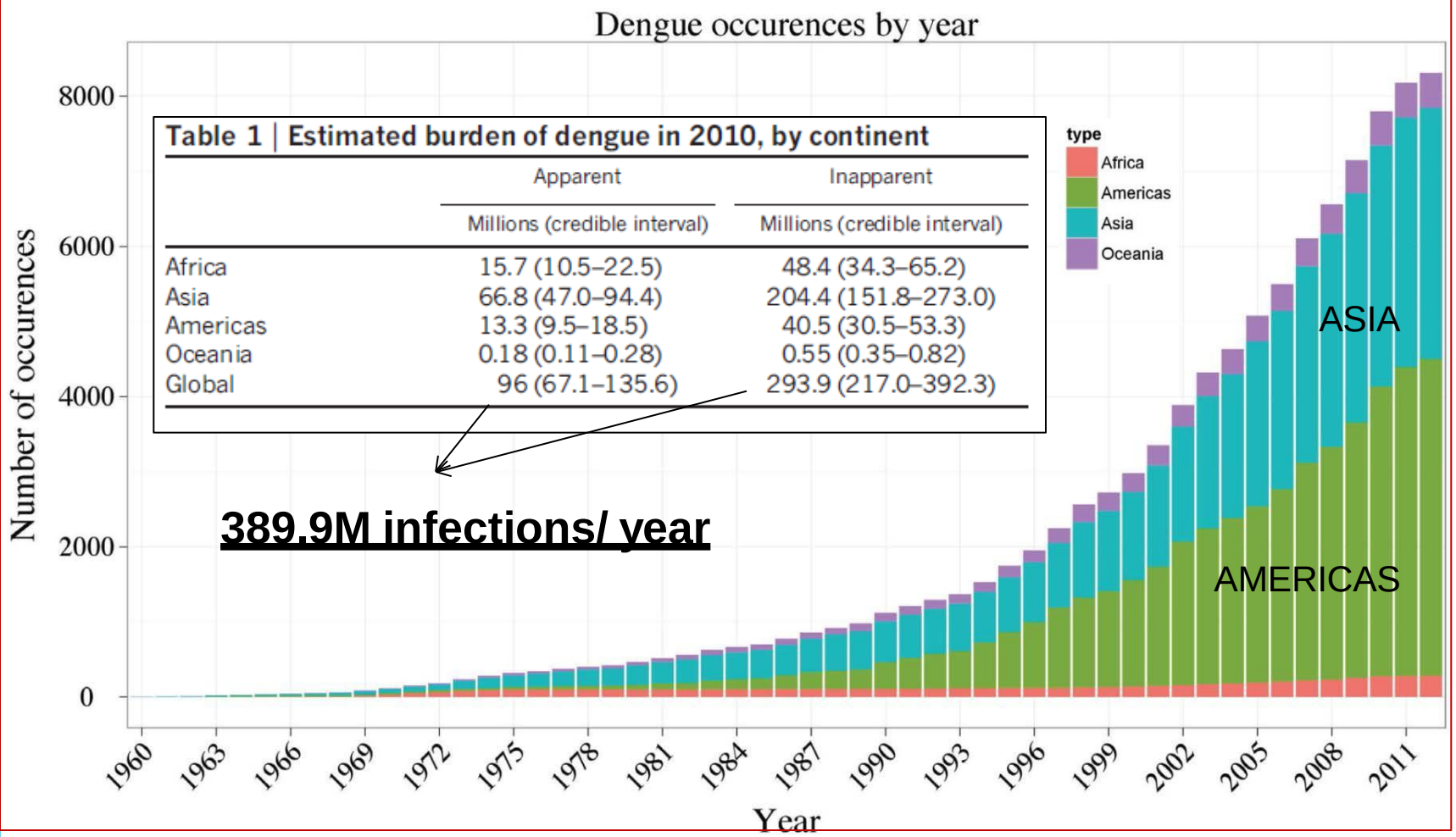
D. Gubler

Dengue Burden

Under-estimated and under-reported

Table 1 | Estimated burden of dengue in 2010, by continent

	Apparent	Inapparent
	Millions (credible interval)	Millions (credible interval)
Africa	15.7 (10.5–22.5)	48.4 (34.3–65.2)
Asia	66.8 (47.0–94.4)	204.4 (151.8–273.0)
Americas	13.3 (9.5–18.5)	40.5 (30.5–53.3)
Oceania	0.18 (0.11–0.28)	0.55 (0.35–0.82)
Global	96 (67.1–135.6)	293.9 (217.0–392.3)



389.9M infections/ year

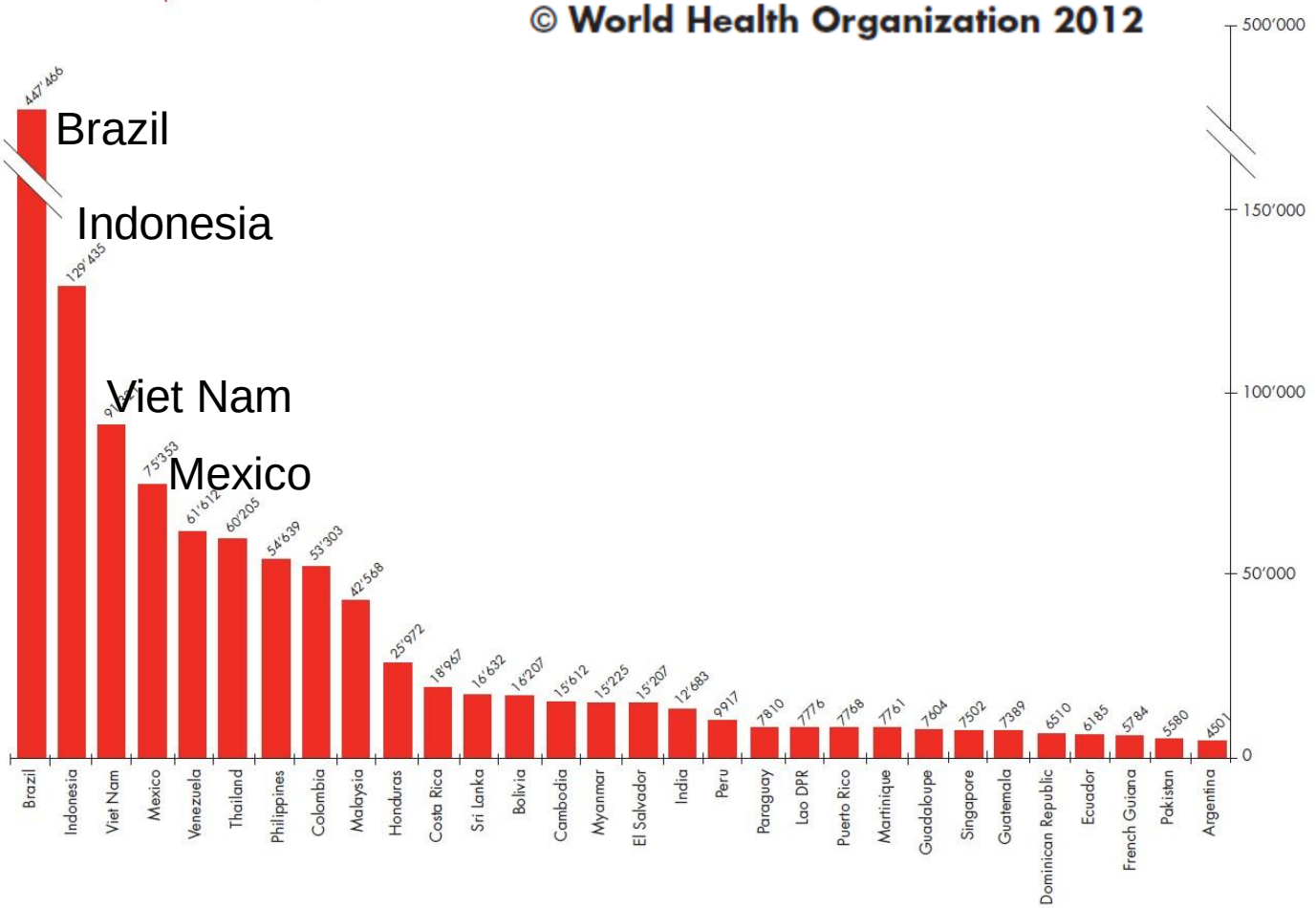
Bhatt et al., Nature. 2013 Apr 7.

2012–2020

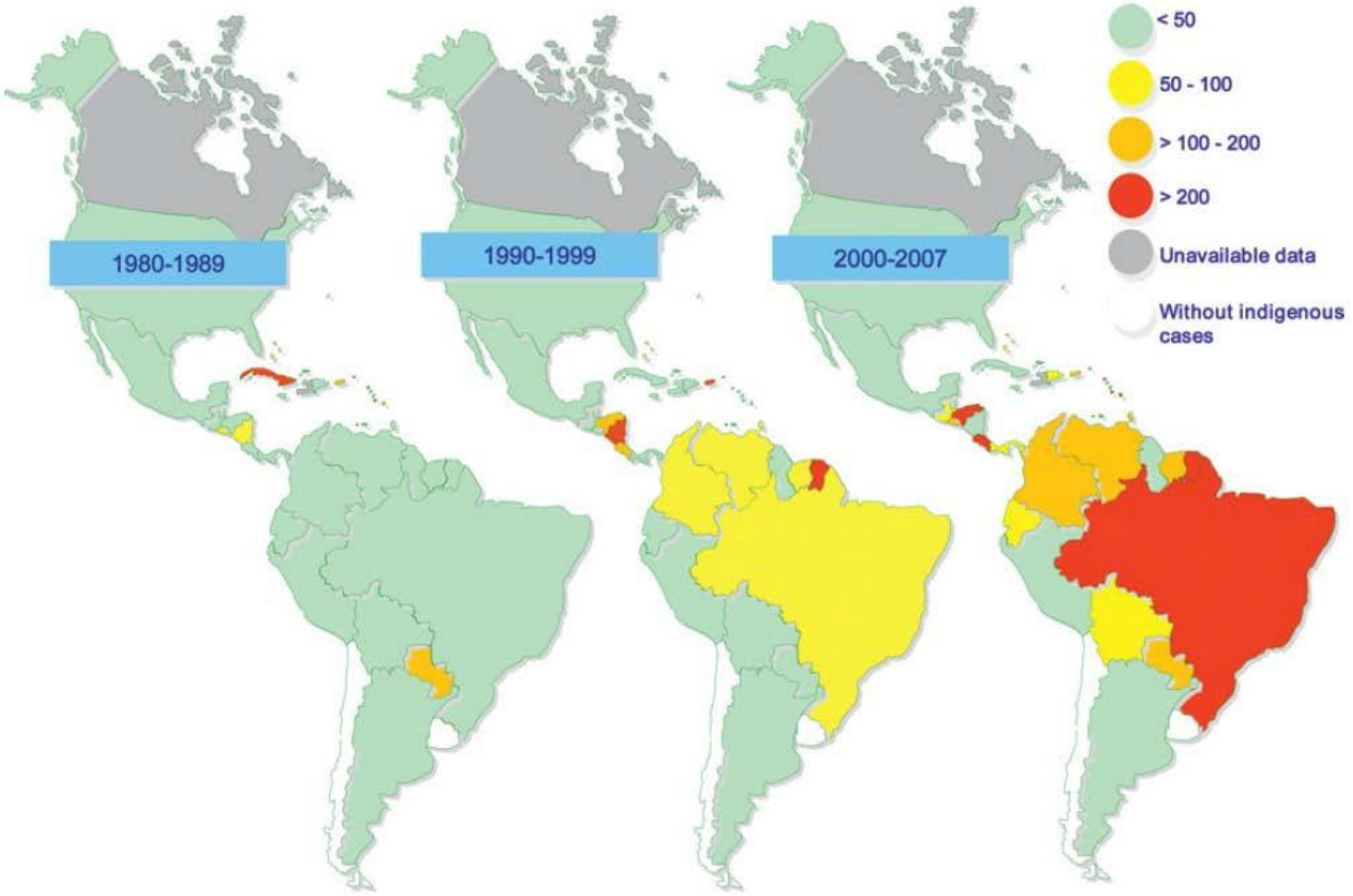
GLOBAL STRATEGY FOR DENGUE PREVENTION AND CONTROL

Figure 3. Average number of dengue cases in 30 most highly endemic countries/territories as reported to WHO, 2004–2010

© World Health Organization 2012



Average dengue incidence /100,000 by country, 1980–2007



Am. J. Trop. Med. Hyg., 82(1), 2010, pp. 128–135

PUBLIC HEALTH 127 (2013) 11–17

Middle East
Pakistan

Table 1 – Confirmed cases and deaths from 2006 to 2011 in the affected areas of Pakistan.

Year	Khyber Pakhtunkhwa		Sindh				Punjab			
			All parts		Karachi		All parts		Lahore	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
2006[a]	31	1	1500	50	1500	50	800	1	400	0
2007[a]	0	0	950	22	950	20	258	0	258	0
2008[a]	30	4	585	6	585	6	1450	20	1358	9
2009[a]	100	7	550	7	550	7	300	2	300	2
2010[b]	0	0	5000	35	4500	16	4000	3	4000	3
2011[b]	296	8	952	18	755	15	21,314	337	17,493	290

a Data collected from National Institute of Health Islamabad.
b Data collected from provincial health departments.

Africa

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 8, August 2011

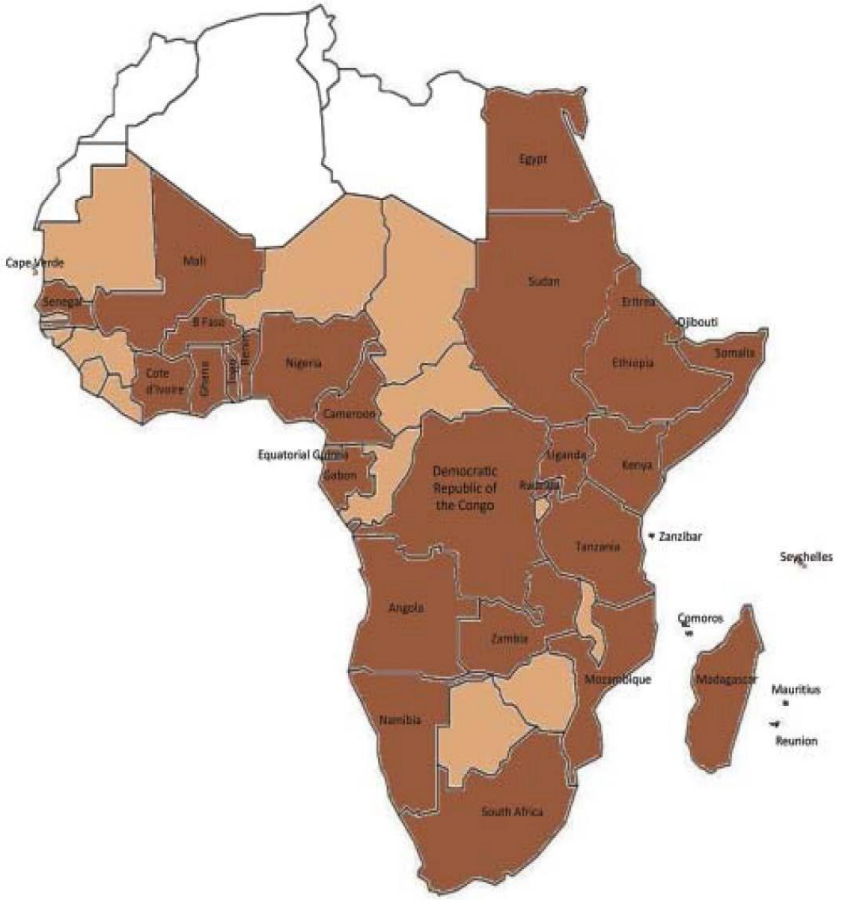


Figure. Dengue and *Aedes aegypti* mosquitoes in Africa. Brown indicates 34 countries in which dengue has been reported, including dengue reported only in travelers, and *Ae. aegypti* mosquitoes. Light brown indicates 13 countries (Mauritania, The Gambia, Guinea-Bissau, Guinea, Sierra Leone, Liberia, Niger, Chad, Central African Republic, Republic of the Congo, Malawi, Zimbabwe, and Botswana) in which dengue has not been reported but that have *Ae. aegypti* mosquitoes. White indicates 5 countries (Western Sahara, Morocco, Algeria, Tunisia, and Libya) for which data for dengue and *Ae. aegypti* mosquitoes are not available.

Brown – dengue reported

Light Brown – dengue not reported but vector exists

White – data not available

High Financial and Human Cost

Economic Impact of Dengue Illness in the Americas

Donald S. Shepard,* Laurent Coudeville, Yara A. Halasa, Betzana Zambrano, and Gustavo H. Dayan
Brandeis University, Waltham, Massachusetts; Sanofi Pasteur, Lyon, France; Sanofi Pasteur, Swiftwater, Pennsylvania

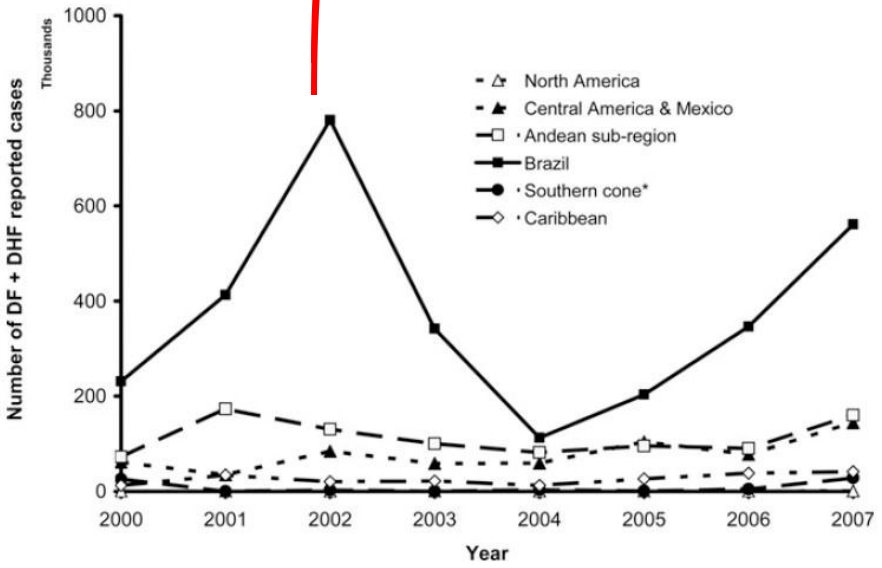


FIGURE 1. Number of dengue reported cases in the Americas from 2000 to 2007.

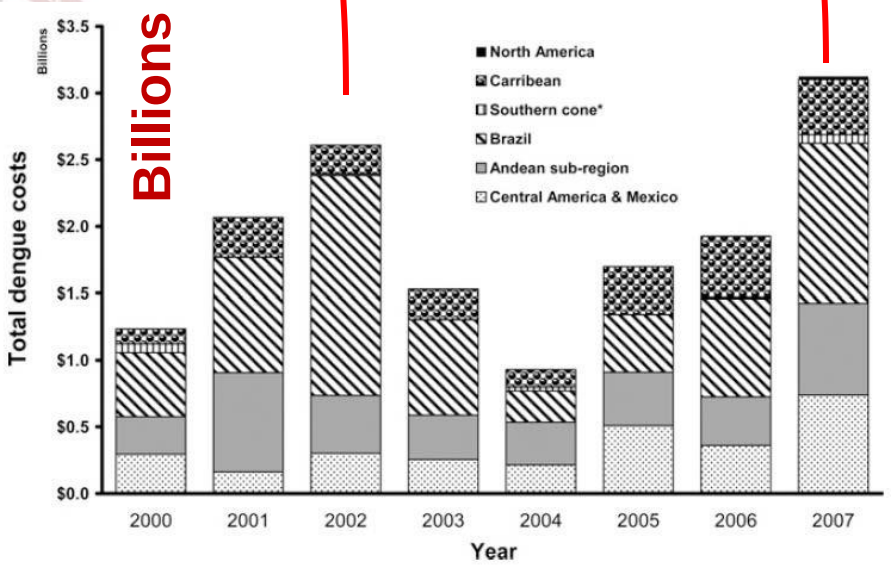


FIGURE 3. Annual economic burden in the Americas from 2000 to 2007 (in 2010 US$).

Am. J. Trop. Med. Hyg., 84(2), 2011, pp. 200–207

Economic and Disease Burden of Dengue in Southeast Asia

PLOS | NEGLECTED TROPICAL DISEASES

Shepard DS, Undurraga EA, Halasa YA (2013) PLoS Negl Trop Dis 7(2): e2055.

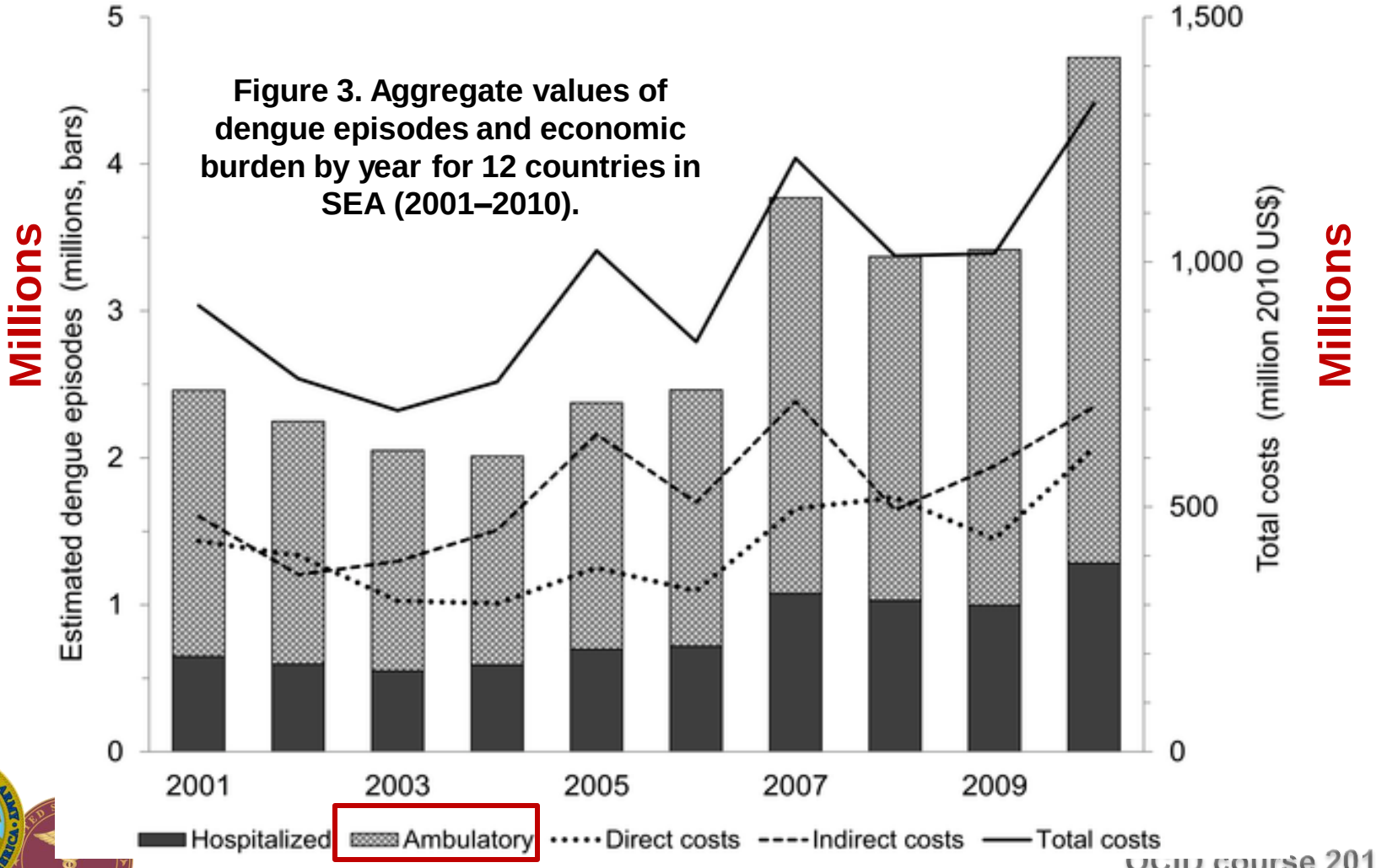
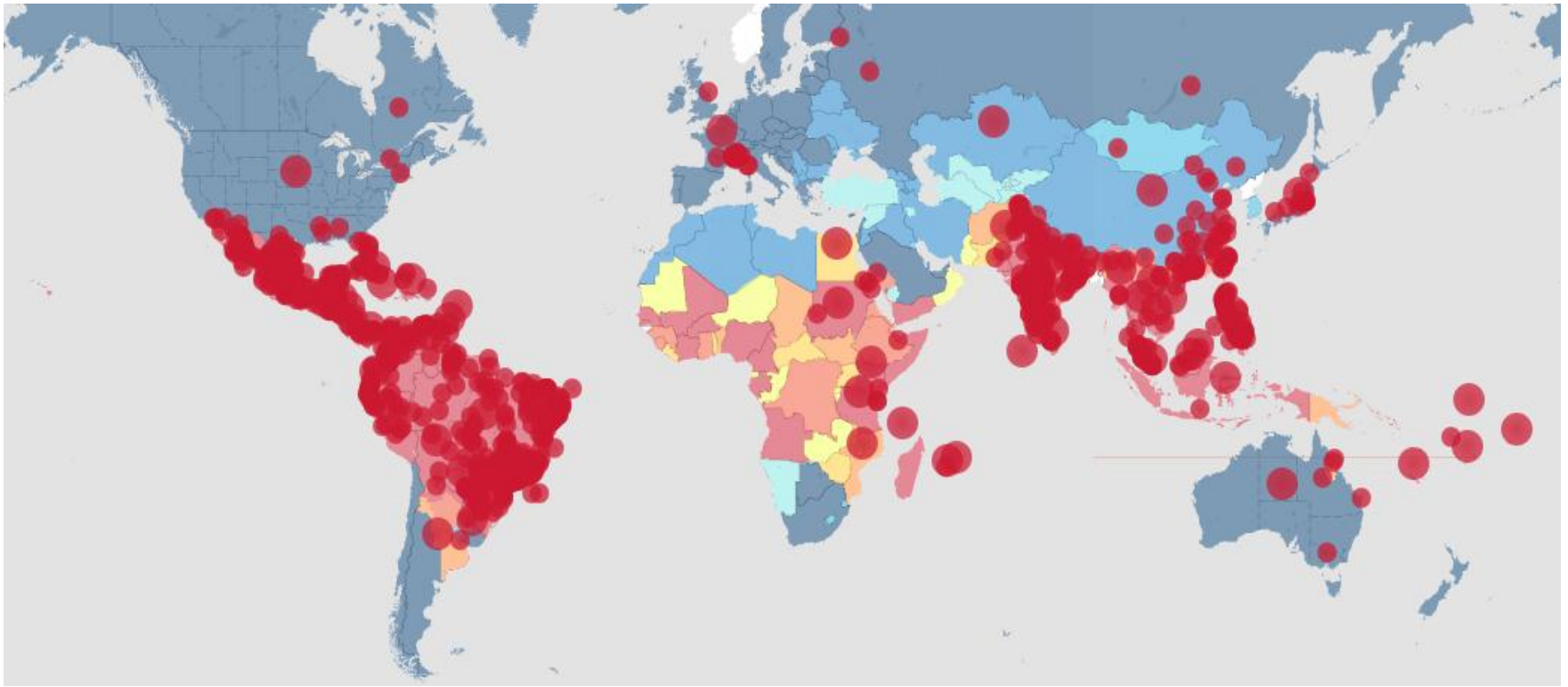


Figure 3. Aggregate values of dengue episodes and economic burden by year for 12 countries in SEA (2001–2010).

CDC Dengue Map – 01MAY – 01NOV 2014



Local level
Country level

Note Cases in Temperate Climates !

Reporting sources – WHO, MOHs, ProMed, GeoSentinel, EuroSurveillance, World Org

In the news …

The Economist | World politics | Business & finance | Economics | Science & technology | Cultur

Dengue fever in Brazil

When it rains, it pours

The welcome return of wet weather has a nasty side-effect

Mar 28th 2015 | SÃO PAULO | From the print edition

Timekeeper | Like 421 | Tweet 84

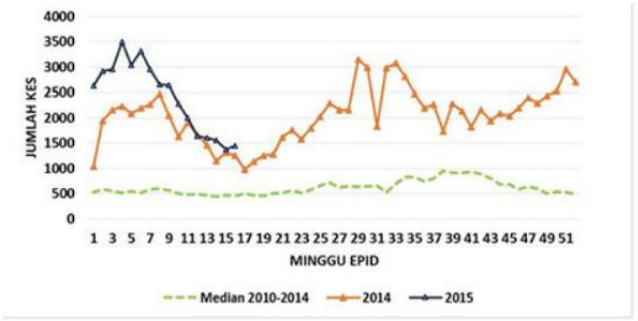
A MOIST March, combined with the wettest February in 20 years, has brought respite to Brazil's parched south-east. Last year's record drought in the region, where two in five Brazilians live and where more than half the country's output is produced, had stretched into January. So the drenching is welcome. But the rains have also stirred up an old scourge: dengue fever, a disease transmitted by mosquitoes. Its early symptoms resemble flu but it can cause fatal internal and external bleeding.

No shelter from the mosquitoes

At least 224,000 cases had been registered across Brazil by March 7th, 162% more than in the same period in 2014, when the dry weather left fewer stagnant puddles in which mosquitoes could breed. The situation is gravest in the state of São Paulo, where 124,000 people have been diagnosed since January, an eightfold increase on last year. Infections have reached epidemic levels in nearly half the state's municipalities (mostly the smaller ones). São Paulo has seen 67 confirmed fatalities. Mercifully, things in the rest of the country are better, meaning that the situation is less severe than the full-blown epidemic that infected 1.5m people in 2013.

Malaysia

As of 25 April 2015, there were 38,517 cases of dengue reported in Malaysia for 2015. This is 33.7% higher compared with the same reporting period of 2014 (n=28,814) (Figure 2). From 19 to 25 April 2015, there were 1,446 cases of dengue reported, 5.2% higher than the same period of the previous week (n=1,370).



Alternative herbal drink introduced to combat dengue fever

…lth, Malaysia (up to 25April 2015)

BY PRIYA PUBALAN - 11 MAY 2015 @ 2:44 PM

Tweet 12 | Recommend | Share 6

BUTTERWORTH: An alternative herbal drink to cure the escalating dengue fever has been introduced.

Thanks to Al Faris Herbs, the 'Sari Daun Betik' is rich in Vitamin C and minerals, made with papaya leaf extract to increase blood platelets in human body.

Al Faris advisor Datuk Dr Shuib Saedin, who is also a medical practitioner, said the drink helps to increase low level of platelets in human body.

"The papaya leaf juice is probably the most well-known alternative treatment for dengue.

"However, it is bitter to consume, especially for children.

"We carried out scientific studies in the past few months and produced this herbal remedy which consists of dates, honey and other vitamins combined with the papaya leaf extract to combat dengue fever," he told reporters today.

Dr Shuib said the results cannot be said to be definitive, due to their small study size, but they are certainly promising.

The product will be available in market starting today and can be found in sundry and retail shops.

It is priced at RM55 per bottle and could last more than a month.

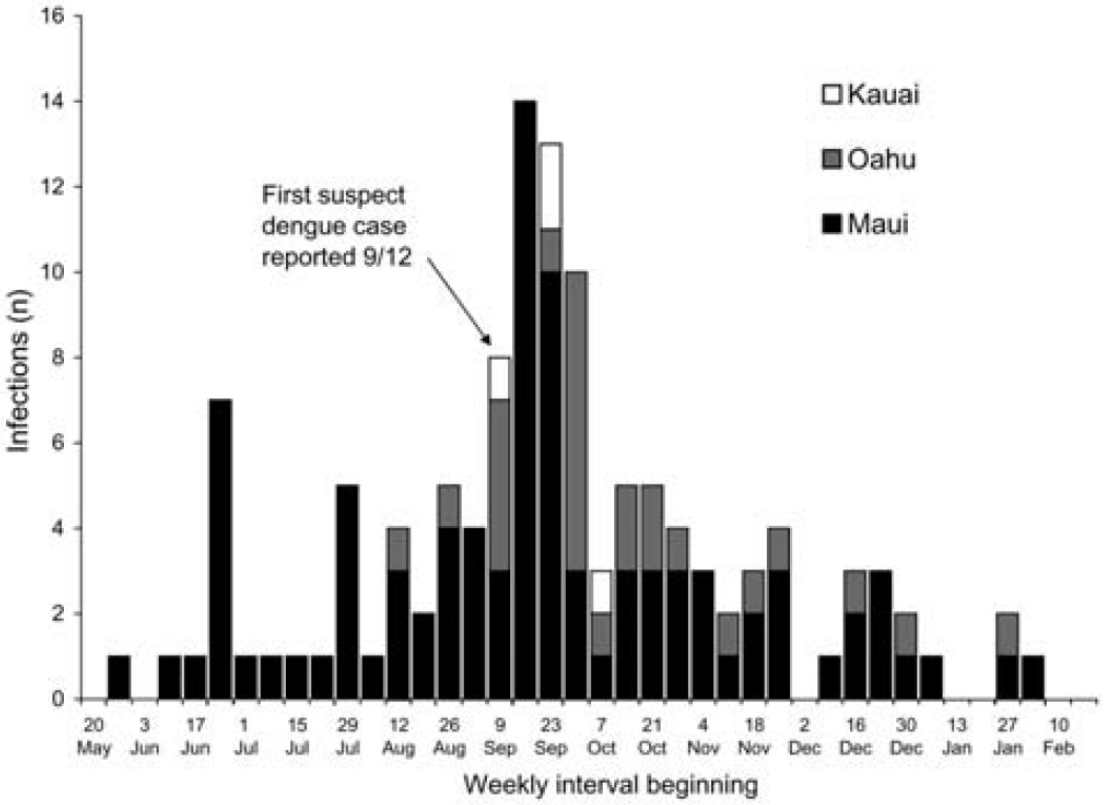
Meanwhile, the latest report from the Health Ministry states that as of May 5, the number of dengue cases has increased to 41,450 cases and 126 deaths nationwide.

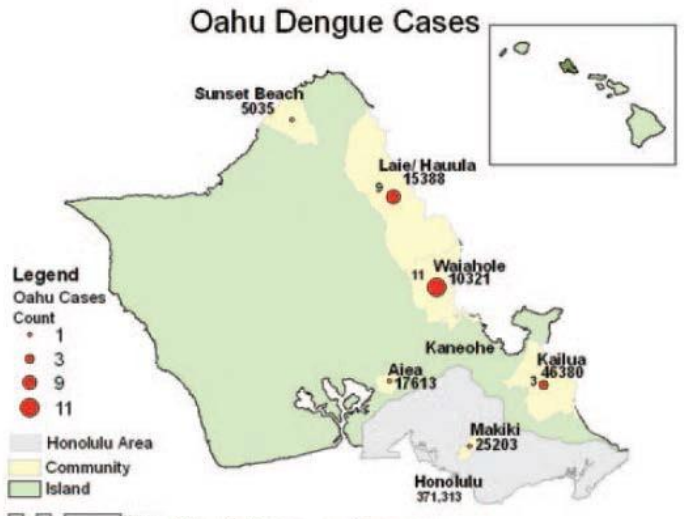
Dengue in the U.S.

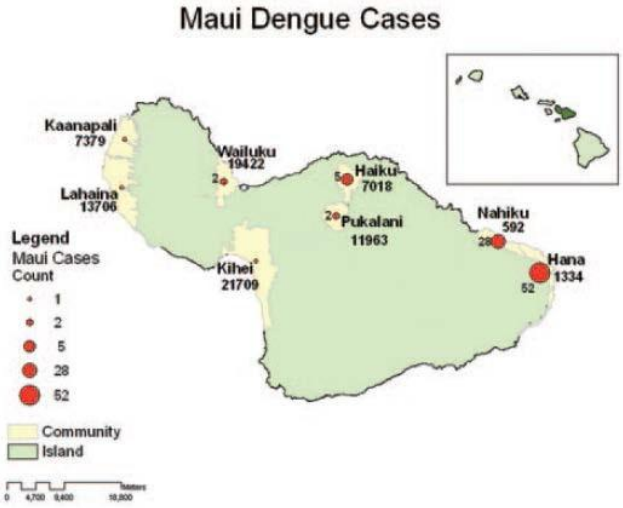
Dengue Fever, Hawaii, 2001–2002

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 5, May 2005

Paul V. Effler,* Lorrin Pang,* Paul Kitsutani,† Vance Vorndam,† Michele Nakata,* Tracy Ayers,*
Joe Elm,* Tammy Tom,* Paul Reiter,† José G. Rigau-Perez,† John M. Hayes,† Kristin Mills,*
Mike Napier,‡ Gary G. Clark,† and Duane J. Gubler*
for the Hawaii Dengue Outbreak Investigation Team[1]







Dengue in the U.S.

Identification of Dengue Fever Cases in Houston, Texas, with Evidence of Autochthonous Transmission Between 2003 and 2005

VECTOR-BORNE AND ZOONOTIC DISEASES
Volume 13, Number 0, 2013
© Mary Ann Liebert, Inc.
DOI: 10.1089/vbz.2013.1413

Am. J. Trop. Med. Hyg., 59(1), 1998, pp. 95–99

DENGUE SURVEILLANCE IN TEXAS, 1995

JULIE A. RAWLINGS, KATHERINE A. HENDRICKS, CHRISTINE R. BURGESS, RICHARD M. CAMPMAN, GARY G. CLARK, LAURA J. TABONY, AND MARY ANN PATTERSON

Infectious Disease Epidemiology and Surveillance Division and Bureau of Laboratories, Texas Department of Health, Austin, Texas; Dengue Branch, Centers for Disease Control and Prevention, San Juan, Puerto, Rico

Dengue Hemorrhagic Fever --- U.S.-Mexico Border, 2005

MMWR
Weekly
August 10, 2007 / 56(31);785-789

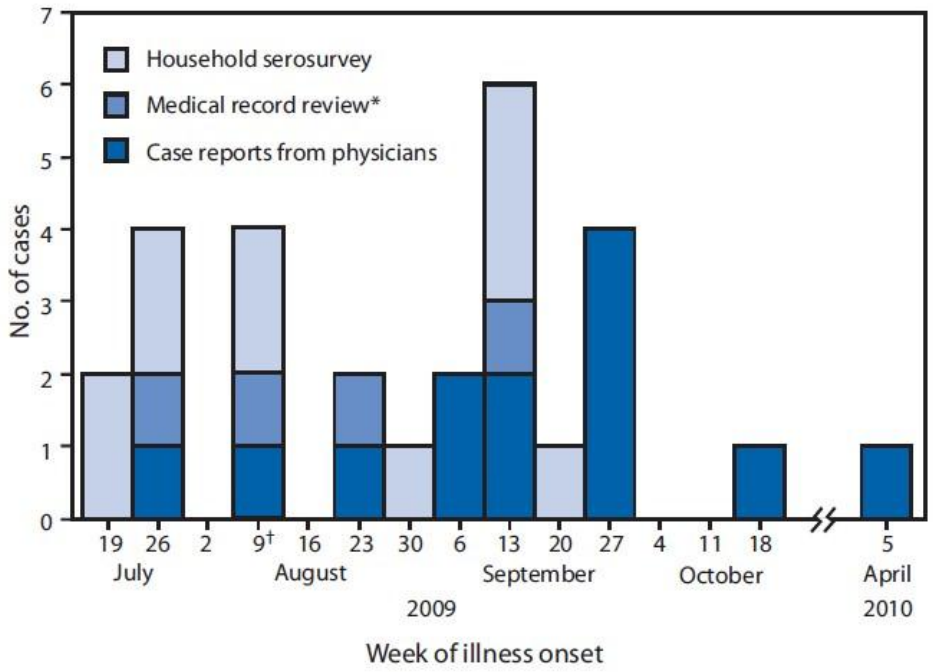
Am. J. Trop. Med. Hyg., 78(3), 2008, pp. 364–369

Epidemic Dengue and Dengue Hemorrhagic Fever at the Texas–Mexico Border: Results of a Household-based Seroepidemiologic Survey, December 2005

Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Weekly / Vol. 59 / No. 19 May 21, 2010

Locally Acquired Dengue — Key West, Florida, 2009–2010

onset and method of identification — Key West, Florida, 2009–2010



* Two cases identified in both household serosurvey and medical record review are shown as record review cases.
† Week of illness onset in index patient.

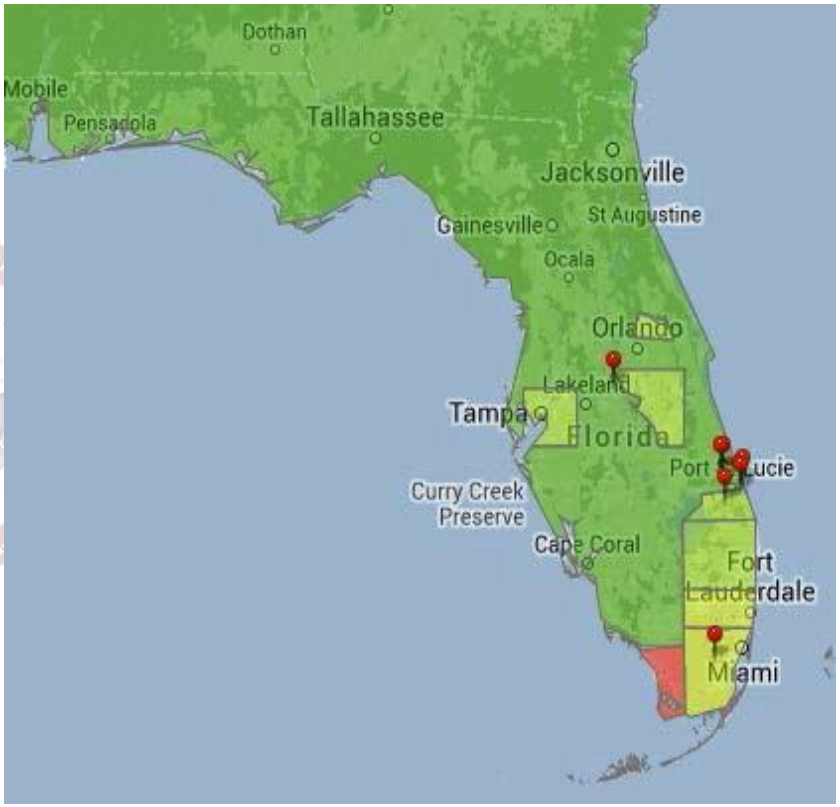
acquired dengue — Key West, Florida, 2009–2010

Characteristic	No.	(%)*
Sex		
Male	19	(68)
Female	9	(32)
Age group (yrs)		
<20	1	(4)
21–40	11	(39)
41–60	11	(39)
>60	5	(18)
Race		
White	24	(86)
Black	3	(11)
Asian/Pacific Islander	1	(4)
Ethnicity		
Non-Hispanic	25	(89)
Hispanic	3	(11)
Symptoms		
Fever	28	(100)
Headache	22	(79)
Myalgia	23	(82)
Arthralgia	18	(64)
Eye pain	14	(50)
Rash	15	(54)
Bleeding	6	(21)

* Percentages might not add to 100% because of rounding.

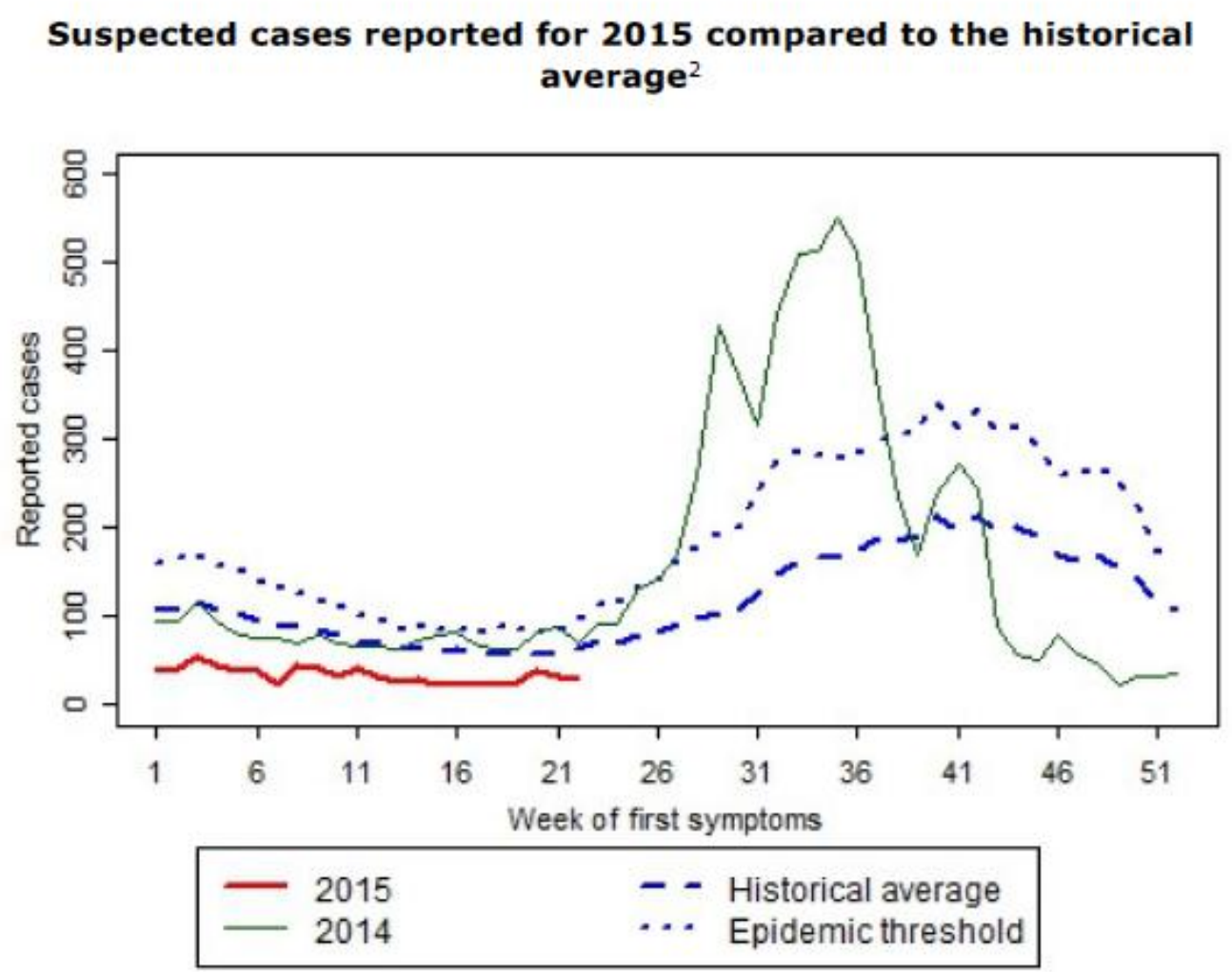
Dengue in the U.S. - Florida 2013

- 2013:
  - 26% of all dengue in the US
  - All 4 serotypes, mostly DENV-1
  - 120 travel related cases
  - 23 locally acquired cases
    - 22 from Martin County
- 2014
  - Few cases
  - Both travel and locally acquired



CDC Dengue Map, 15 OCT 2013

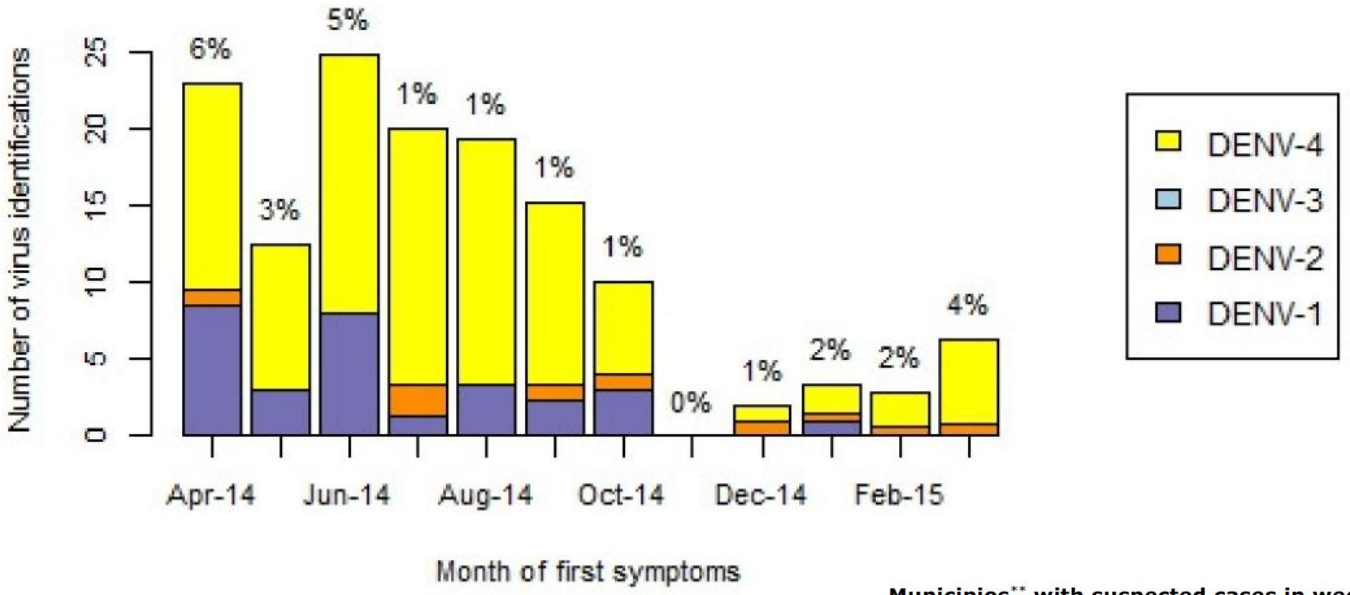
Puerto Rico : 2014 epidemic compared to 2015
(through 6/24/15, CDC)



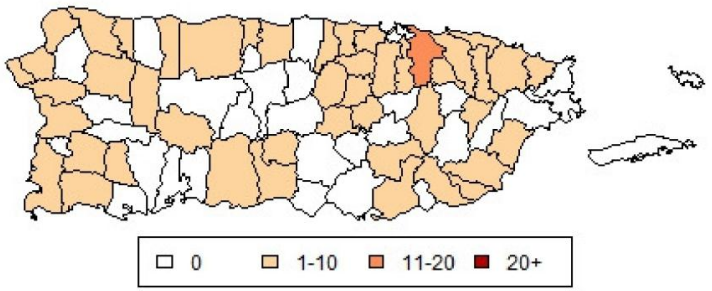
References: CDC Website

Puerto Rico 2014 Epidemic

Total viral identifications in the last 12 months[4]



Municipios with suspected cases in weeks 11-14**



References: CDC Website

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 12, 2006 VOL. 354 NO. 2

Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

David O. Freedman, M.D., Leisa H. Weld, Ph.D., Phyllis E. Kozarsky, M.D., Tamara Fisk, M.D.,* Rachel Robins, M.D., Frank von Sonnenburg, M.D., Jay S. Keystone, M.D., Prativa Pandey, M.D., and Martin S. Cetron, M.D., for the GeoSentinel Surveillance Network†

Table 3. **Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region.***

Syndrome and Cause	All Regions	Caribbean	Central America	South America	Sub-Saharan Africa	South Central Asia	Southeast Asia	Other or Multiple Regions†
			number of cases per 1000 patients with syndrome					
Systemic febrile illness (n=3907)								
Specific pathogen or cause reported‡	594	459	527	446	718	522	547	454
Malaria‡	352	65	133	133	622	139	130	234
Dengue‡	104	238	123	138	7	142	315	35
Mononucleosis (due to Epstein–Barr virus or cytomegalovirus)‡	32	70	69	79	10	17	32	63
Rickettsial infection‡	31	0	0	0	56	10	16	24
Salmonella typhi or *S. paratyphi* infection‡	29	22	25	17	7	141	26	24
No specific cause reported‡	406	541	473	554	282	478	453	546

‡ P<0.01 for the comparison among regions.

"With respect to specific diagnoses, malaria was one of the three most frequent causes of systemic febrile illness among travelers from every region, ***although travelers from every region except sub-Saharan Africa and Central America had confirmed or probable dengue more frequently than malaria****."*

Dengue and US Military Operations from the Spanish–American War through Today

Robert V. Gibbons, Matthew Streitz, Tatyana Babina, and Jessica R. Fried

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 4, April 2012

Figure 1. Captain Percy Ashburn.

Figure 3. Lieutenant Commander J.F. Siler.


Figure 6. Airplane spraying of DDT over Manila, the Philippines, 1945.

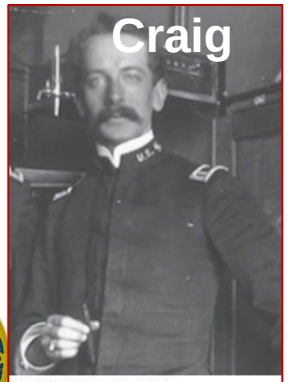


Figure 2. First Lieutenant Charles Craig.

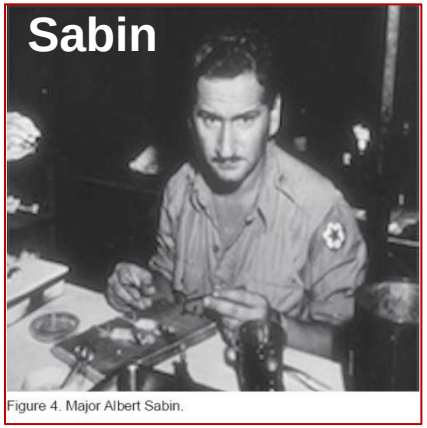


Figure 4. Major Albert Sabin.

Dengue U.S. Military Impact

- WWII: >85,000 U.S. cases
  Outbreaks: 80% attack rate
  Saipan: 20,000 cases in a 3 month period

- Vietnam (1966): most prevalent cause of FUO

- Somalia (1992-93): 59 cases/289 febrile troops

- Haiti (1994): Most common infectious cause of hospital admission

Dengue Risk / Threat to DoD

- **Prevalence and Risk to Soldiers (2003-2012)**
  - Total Cases: 631
    - Active Duty: 177; Reserve: 35; MHS Beneficiaries: 419
    - No record of attributable deaths
  - Dengue Mission Impact Projections
    - Not severe: hospitalized ~5-7 days, low functioning ~14-28 days
    - Severe: evacuation to MTF, ICU care?, death?, LDD >1 month
  - Deployment
    - DODSR: 500 samples, deployed between 2006-2008
      - 11.2% seroprevalence of dengue antibody
      - 2.4% with monovalent profile (high risk with next infection)

References: *Dengue Tetravalent Vaccine CDD; ⁺DMSS

Seroprevalence of DENV Exposure in Deployed Personnel

- DODSR, 1000 samples, first time deployers, 2008-2011
- 250 samples selected per COCOM
- Tested for presence of neutralizing antibody by microneut assay
- Overall 7.6% seroprevalence rate of past dengue exposure
- 1.5% seroconversion rate during deployment (first infection)
- Increased self report of fever during deployment in those with antibodies

Seroprevalence Based on 1,000 Post-Deployment Samples in First Time Deployers

	Central America	South America	Asia	Africa	Total
Percent	4.8%	12.4%	7.2%	6.0%	7.6%

DENV Exposure in USASOC Personnel

- USASOC and WRAIR Viral Diseases threat characterization
- 1027 samples tested since 2010
- Pre/post-deployment sample collection in SOC personnel
  - Tested for presence of neutralizing antibody by MN assay
  - 13.73% are seropositive to at least one DENV serotype
  - 9.35% are tetravalent responses
  - 4.38% are monolavent, bivalent or trivalent responses
  - Ongoing testing
- **USASOC personnel are highly primed to dengue, a proportion are in high risk category for severe disease with secondary infection**

DOD Infectious Disease Threats

Disease	2010 COCOM panel rank	ID-IDEAL Rank
Malaria	1	2
Dengue	**2**	**3**
Diarrhea, bacterial	3	1
MDR wound pathogens	4	NA
Leishmaniasis	5	19
Q fever (Coxiella burnetti)	6	26
Norovirus / viral diarrhea	7	NA
Influenza	8	NA
Leptospirosis	10	7
Diarrhea, protozoal	11	11
TB	12	NA
CCHF	13	10
HIV	14	8
HFRS	15	17
Chikungunya	16	4
Meningococcal meningitis	17	20
Plague	18	27
Ricketsioses	19	18
Viral encephalitides	20	NA

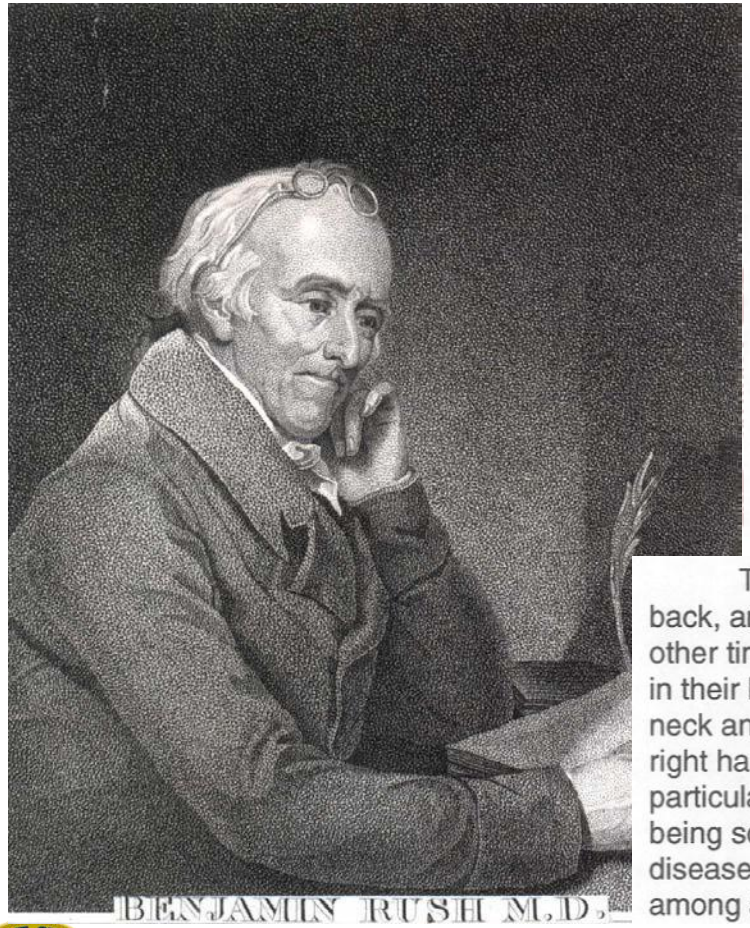
Case Presentation

- 18 year old native from Thailand (moved to US at 10 years of age) presents in August with 2 days of illness including fever, headache, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. You suspect he has a dengue infection. He is tolerating PO intake without vomiting and is urinating. Vital signs except for temperature (102.5F) are in the range of normal. Mucous membranes are moist, skin turgor is normal, abdominal exam is normal, and lungs are clear. A CBC reveals a low WBC (3.5k) but otherwise is within normal limits. Electrolytes are normal.

- What is the most reasonable initial management strategy?

  - 1. treat as outpt, provide NSAIDS, encourage PO fluids
  - 2. treat as inpt, provide 1L NS bolus, monitor in ICU setting
  - 3. treat as outpt, provide acetaminophen, encourage po fluids, F/U
  - 4. treat as inpt, encourage PO fluids, perform q6 hr HCT evaluations

Clinical Phenotype



AN

ACCOUNT

OF THE

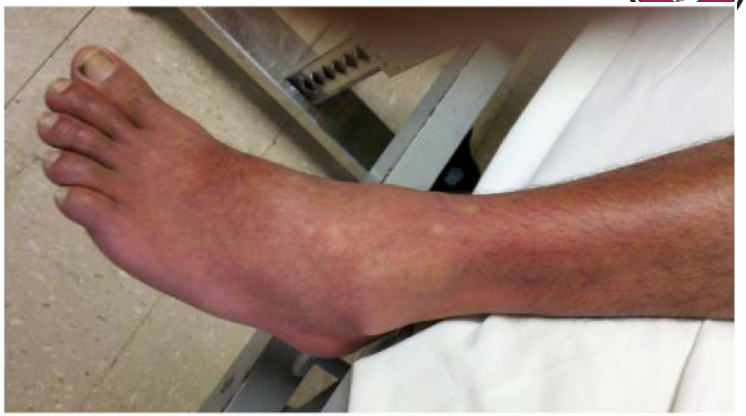
Bilious Remitting Fever,

AS IT APPEARED IN PHILADELPHIA, IN THE SUMMER AND AUTUMN OF THE YEAR 1780.

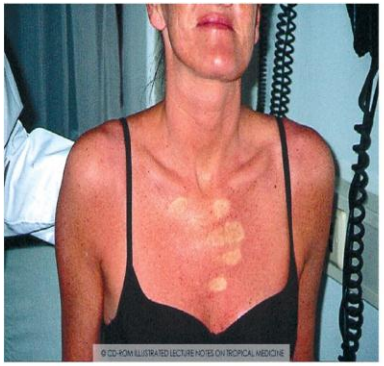
The pains which accompanied this fever were exquisitely severe in the head, back, and limbs. The pains in the head were sometimes in the back parts of it, and at other times they occupied only the eyeballs. In some people, the pains were so acute in their backs and hips, that they could not lie in bed. In others, the pains affected the neck and arms, so as to produce in one instance a difficulty of moving the fingers of the right hand. They all complained more or less of a soreness in the seats of these pains, particularly when they occupied the head and eyeballs. A few complained of their flesh being sore to the touch, in every part of the body. From these circumstances, the disease was sometimes believed to be a rheumatism. But its more general name among all classes of people was, the *Break-bone fever.*

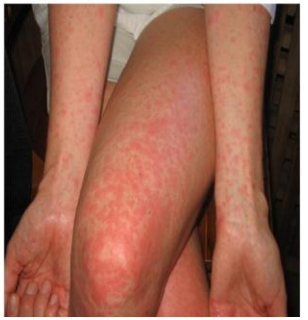
Suspecting Dengue

- Travel to endemic region
- Incubation: 4-7 days, range 3-14 days
  - Travel > 14 days prior = other dx
- Classic “Breakbone fever”
  - 15-60% of patients
  - Myalgias, arthralgias
  - Headache, retro-orbital pain
  - Rash
    - 2-5 days AFTER fever onset
    - More common in primary infection
  - Nausea, vomiting, abdominal pain
    - More common in secondary infection



Classic dengue rash: “islands of white in a sea of red.” Patient with acute dengue fever, Puerto Limon, Costa Rica, 2010





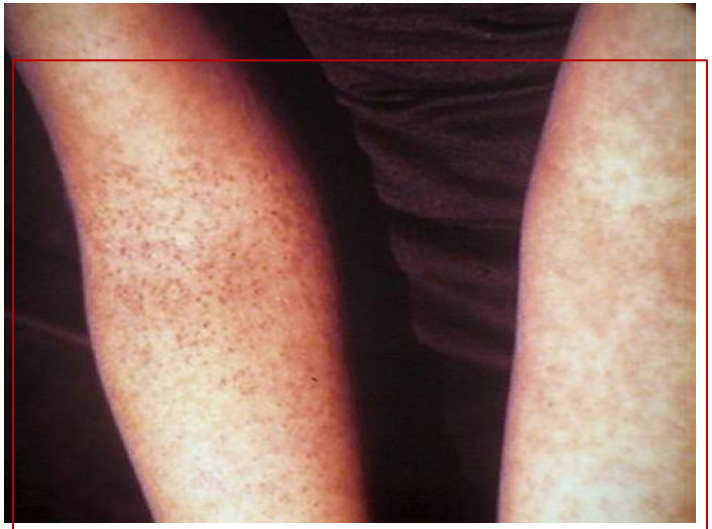
http://www.itg.be/itg/DistanceLearning/LectureNotesVandenEndenE/imagehtml/ppages/CD 1038 061c.htm. Used with permission

Diagnosing Dengue

- Maintain high degree of suspicion
  - Geographic location
  - Clustering of cases
- History and physical
  - Clinical presentation
  - Vital signs (HR, BP, Temp)
  - Dengue tourniquet test (TT)
- Clinical lab assessment
  - CBC (WBC, HCT, PLT), AST/ALT
- Dengue tests in US
  - IgM capture ELISA
  - CDC RT-PCR
- Dengue area, +Clinical, +TT, WBC<5k = High PPV (~70%)

Dengue Tourniquet Test

- Measure BP
- SBP + DBP / 2 = target insufflation pressure for test
- Inspect area near antecubital fossa
  - You will assess delta before / after
- Inflate to target pressure
- Hold for 5 minutes
- Remove cuff
- Reassess antecubital fossa
- Count # of petechiae in 2.5 cm^2 area
- ≥10 new petechiae is positive
- **TT measures capillary fragility, severe disease predictor?**

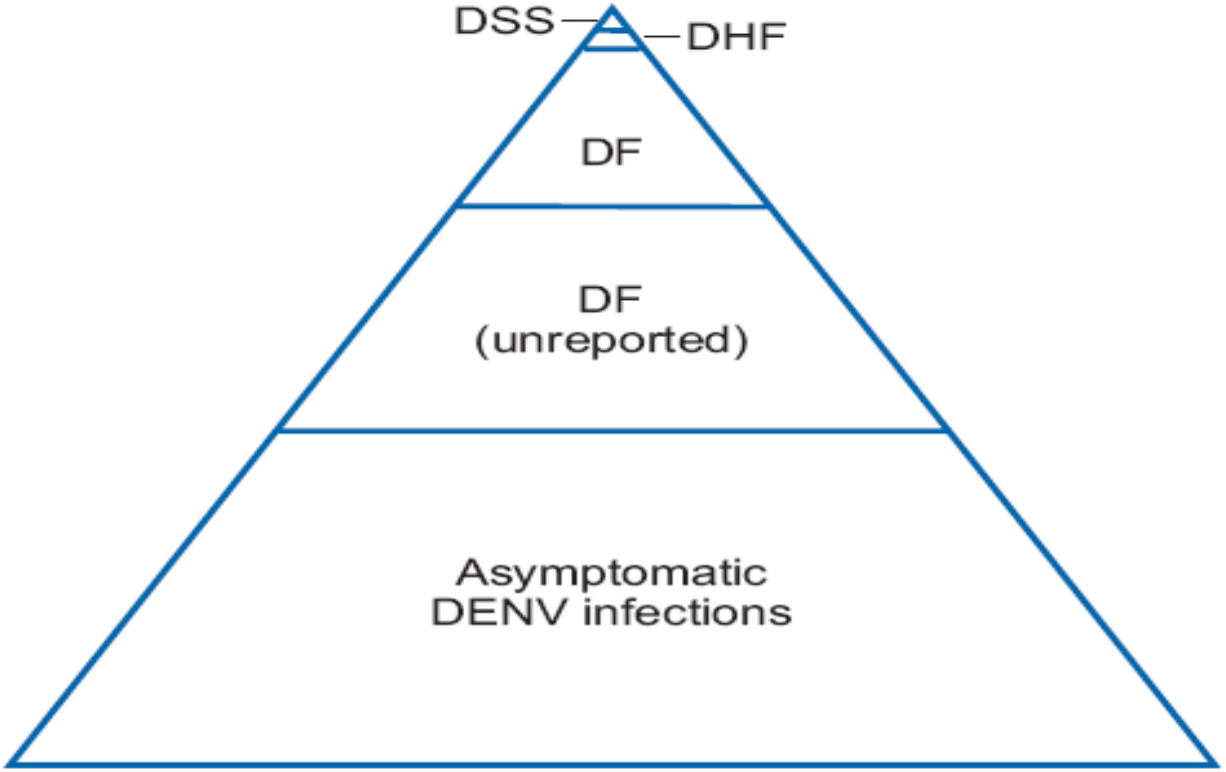


1997 WHO Dengue Fever Case Definition

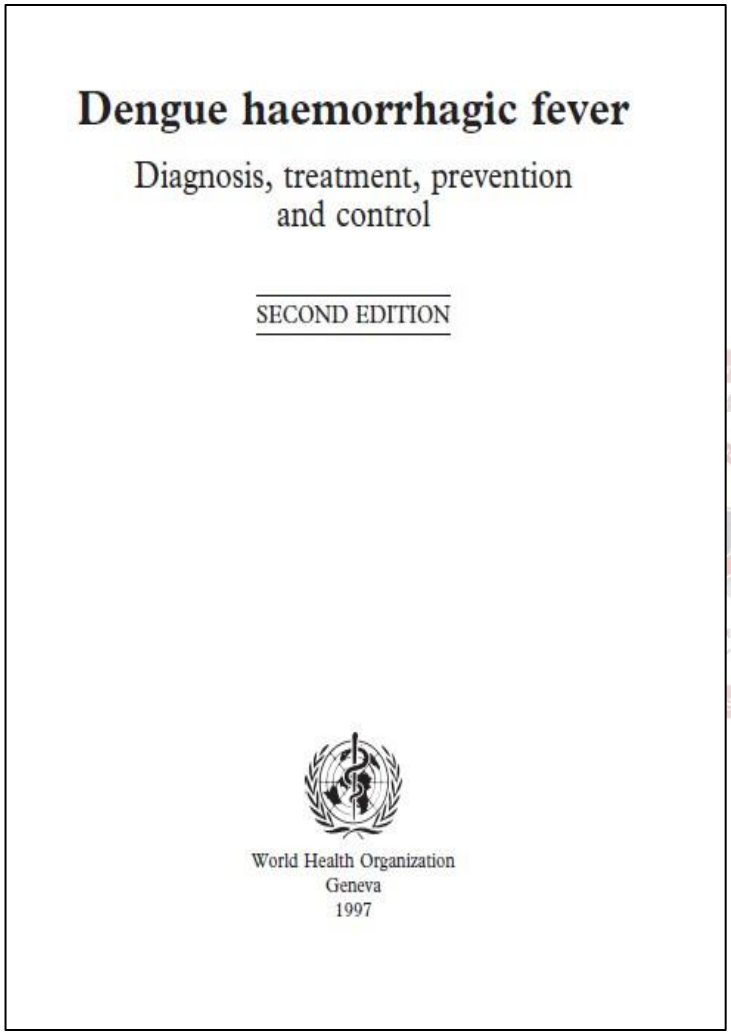
- **Dengue Fever (DF)** = Acute febrile illness + fever and AT LEAST 2 of:
  - Retro-orbital or ocular pain, headache, rash, myalgia, arthralgia, leukopenia, or hemorrhagic manifestations but not meeting the case definition of dengue hemorrhagic fever.
- **Dengue Hemorrhagic Fever (DHF)**= DF + ALL bellow
  - Fever 2-7 days,
  - hemorrhagic manifestation or a positive tourniquet test
  - Thrombocytopenia (≤100,000 cells per mm3)
  - Evidence of plasma leakage shown by hemoconcentration
- **Dengue Shock Syndrome (DSS)** = DHF + circulatory failure

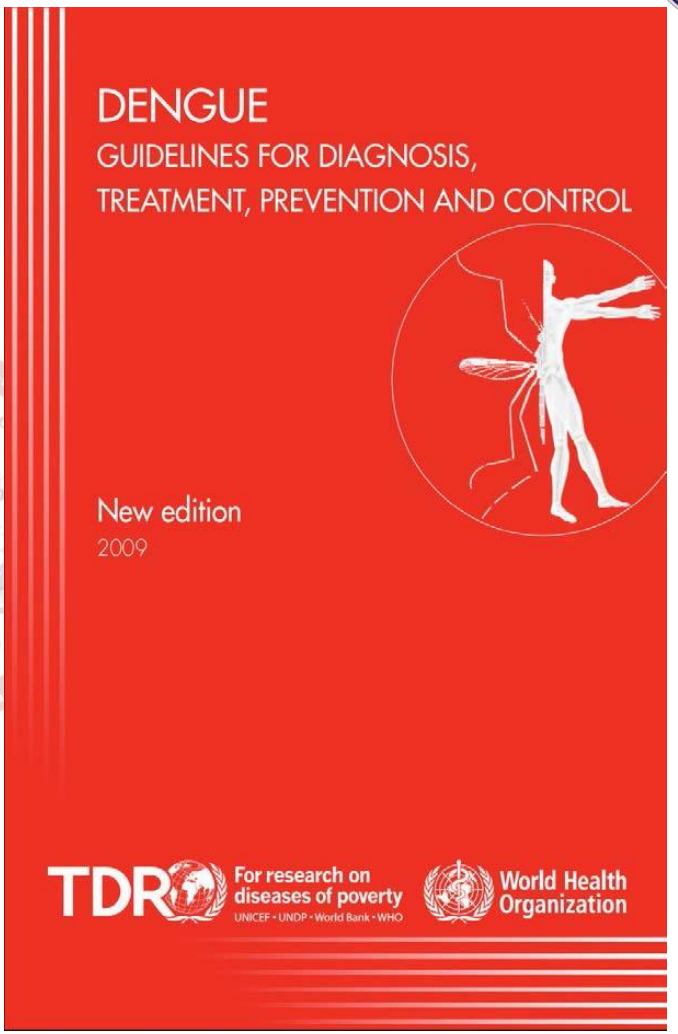
- Definition revised to improve care to those not meeting DHF definition, emphasize plasma leakage as a sign, and improve disease capture and reporting.

Clinical Phenotypes



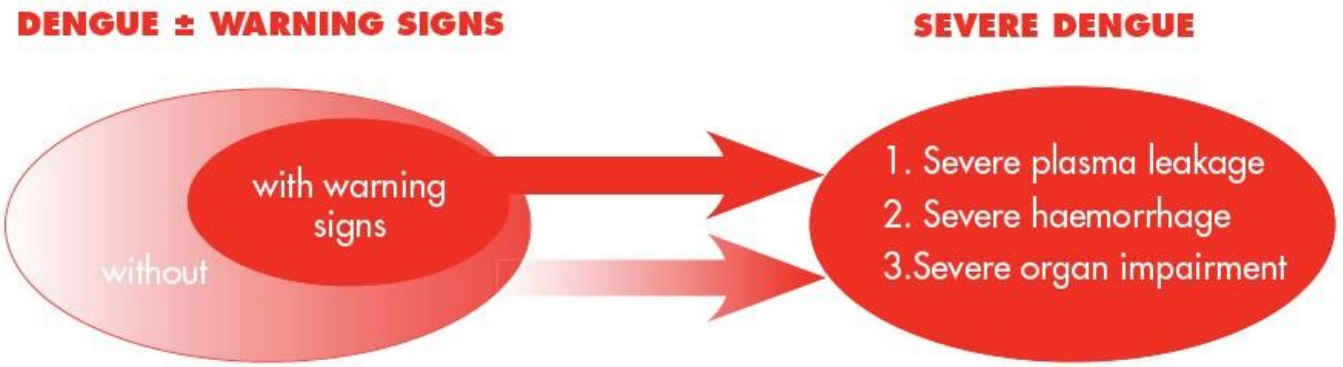
Annu. Rev. Microbiol. 2008. 62:71–92





http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf

Suggested Dengue Case Classification and Levels of Severity



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

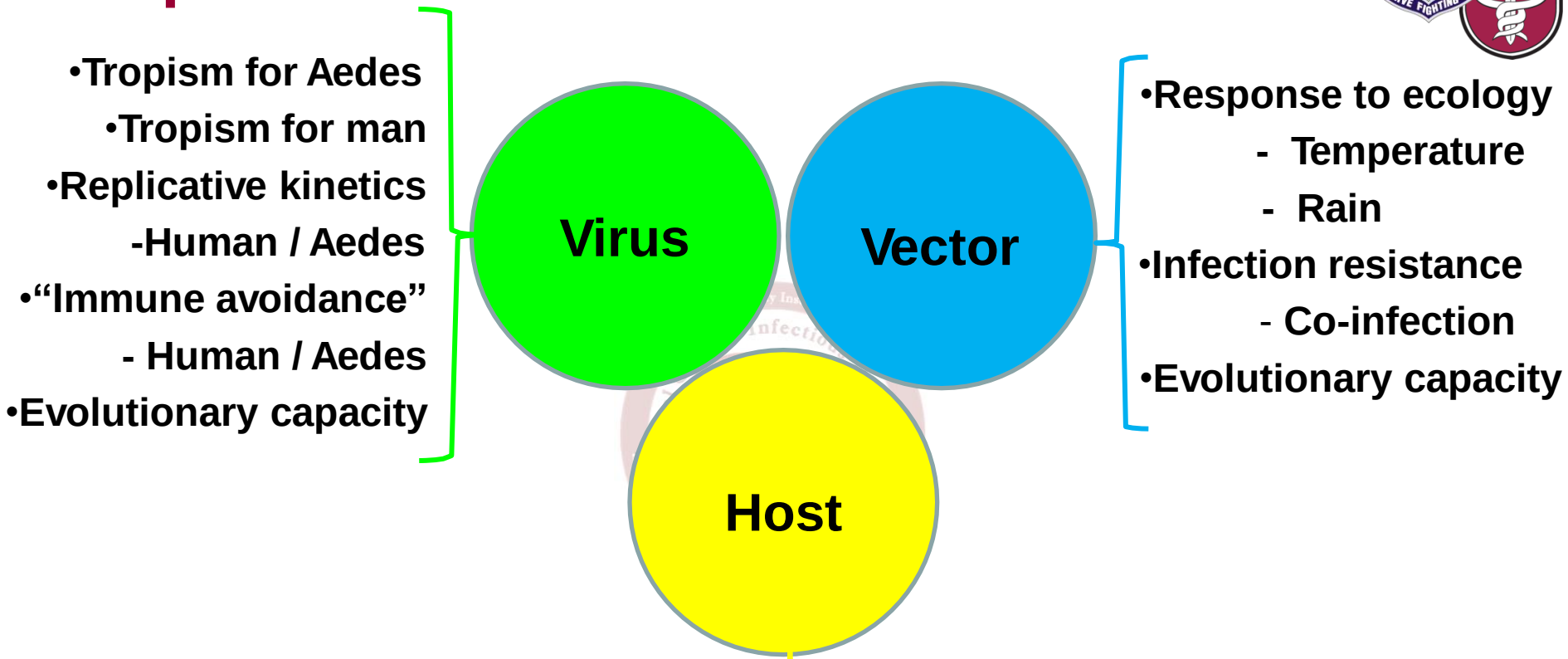
Severe organ involvement

- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

Pathophysiology

Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)

Exposure Determinants – Infection Risk



•Immune profile (dengue, other flavivirus)

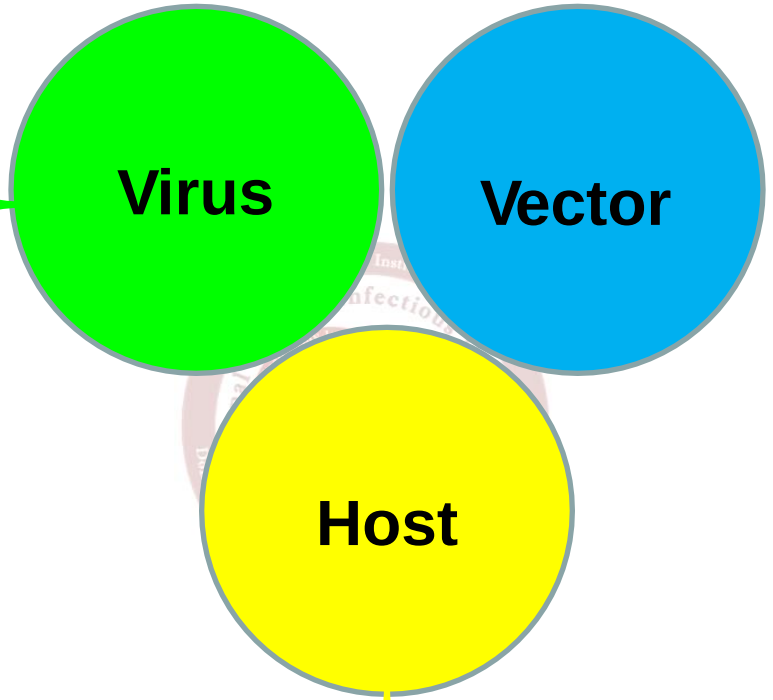
•Vector exposure dynamics (duration, concentration)

•"Neighbors" infection status

•Activities of daily living (who, what, where, when)

Infection Outcome Determinants – Disease Risk

- •DENV type
- •DENV genotype
- •Replicative kinetics
- •Immune evasion
- •Target cell tropism
- •Evolutionary capacity
- •Sequence of infection



- •Salivary proteins

- •Immune profile (first infection, humoral, cellular)
- •Demographic (age, race, genetic background [HLA])
- •Co-morbidities
- •Medical system sophistication treating dengue

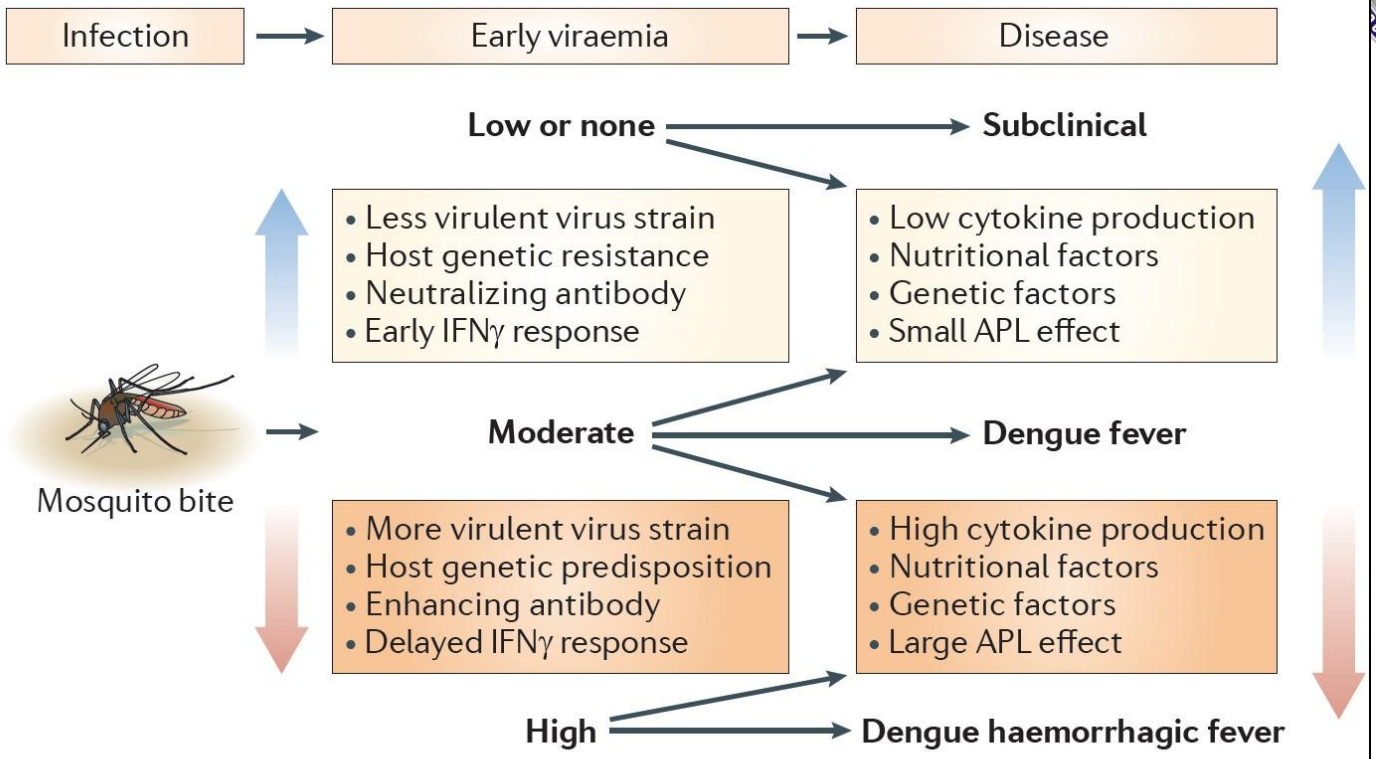


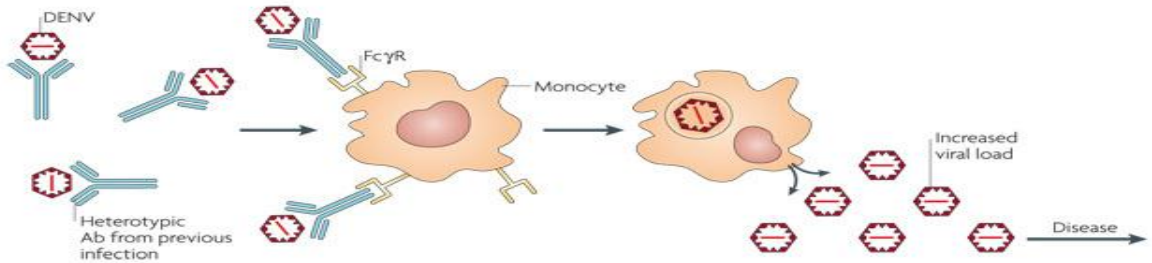
Figure 4 | **A balance between favourable and unfavourable factors determines the clinical outcome of dengue virus infection.** Virus inoculation by *Aedes aegypti* mosquitoes results in viral dissemination, which in turn results in disease manifestations; high virus titres are necessary but not sufficient to cause severe disease. Viral and host factors affect early viral replication and influence the level of viraemia. Other host factors affect the levels of production of various cytokines (such as interferon-γ (IFNγ) and tumour necrosis factor (TNF)) and determine the severity of illness for any given level of viraemia. APL, altered peptide ligand.

Disease Risk – What We Know

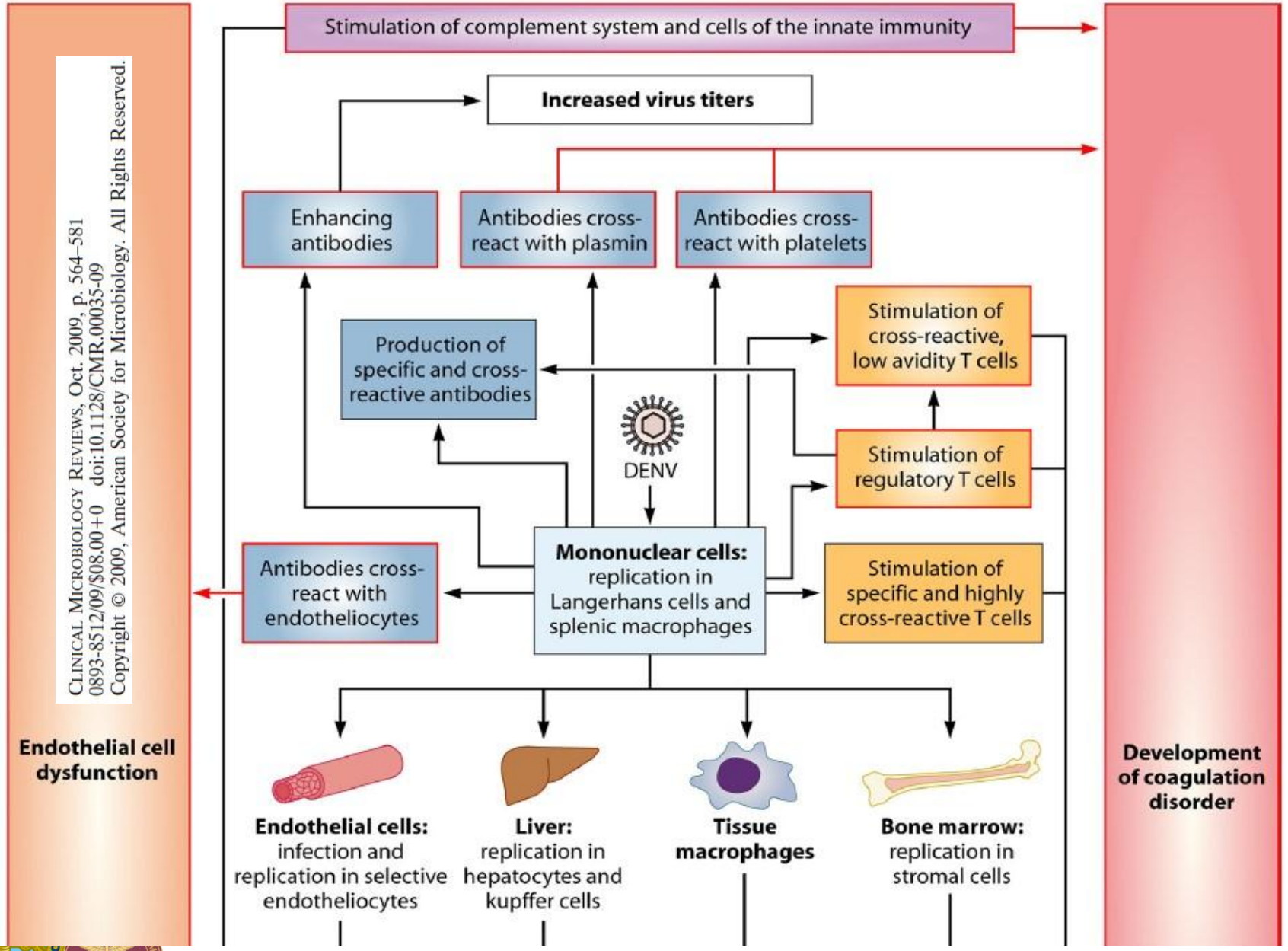
- Virulence likely serotype (DENV 2) and genotype (Asian strains) specific
- Risk for severe disease declines with age
- Severe disease appears less common in malnourished children
- Host (human) genetic variation such as HLA type

Secondary Infection

- Increased risk of severe dengue if infected with a different serotype
- Heterotypic antibodies protective against all 4 serotypes for a brief period
  - At least 3 months
- Antibody Dependent Enhancement
- Serotype sequence and virus genotype may be important
  - DENV 1 followed by DENV 2
    - Asian DENV 2 genotype but not American (Watts 1999)
- Host Specific
- 3rd or more heterotypic infections have much lower rates of severe disease
- Multiple serotypes / genotypes circulating in one area
- Interaction between dengue and immune system is complicated



Whitehead, S. S. *et al.* Prospects for a dengue virus vaccine. *Nature Reviews Microbiology* 5, 518–528 (2007)



CLINICAL MICROBIOLOGY REVIEWS, Oct. 2009, p. 564–581
0893-8512/09/$08.00+0 doi:10.1128/CMR.00035-09
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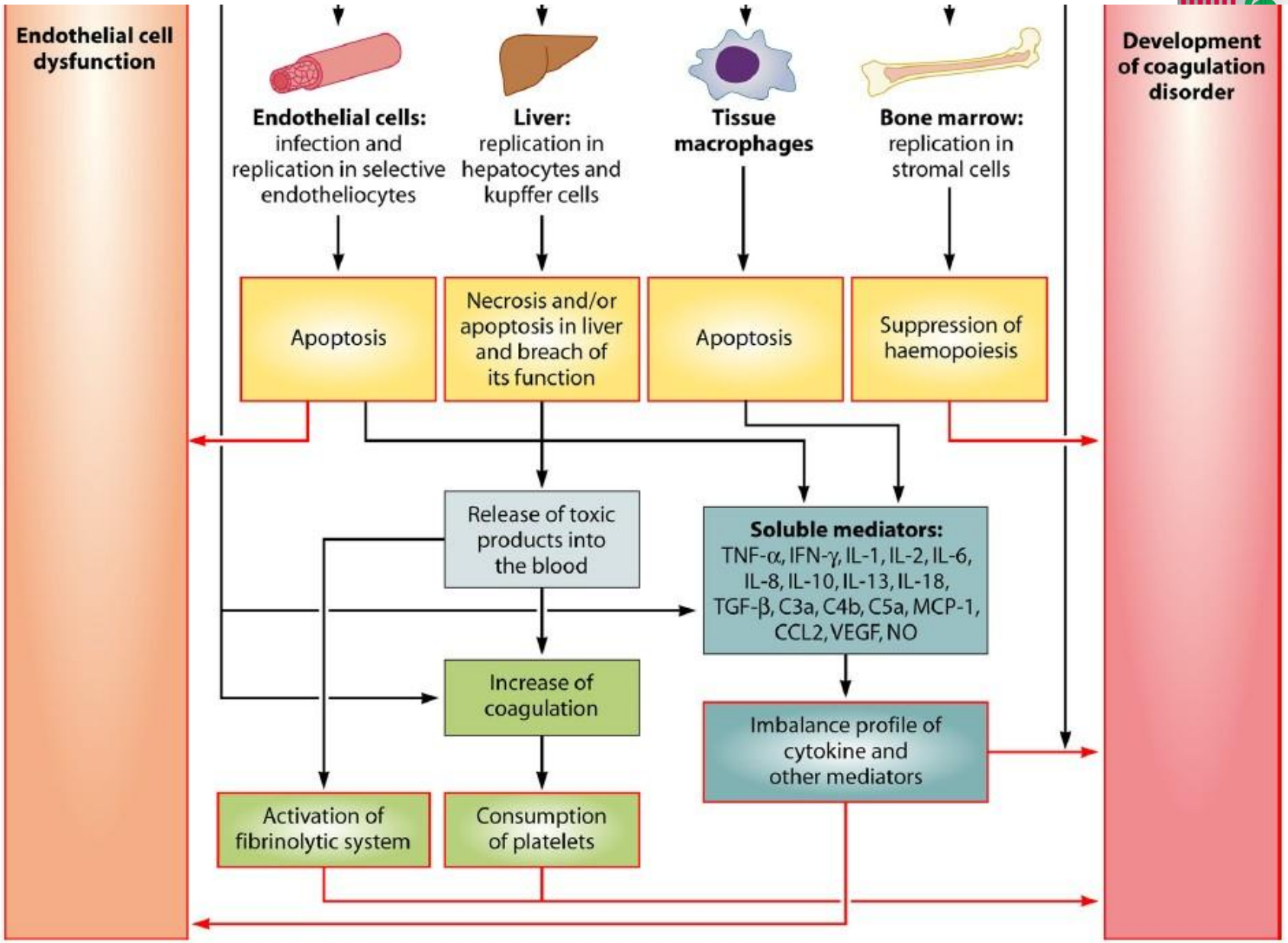
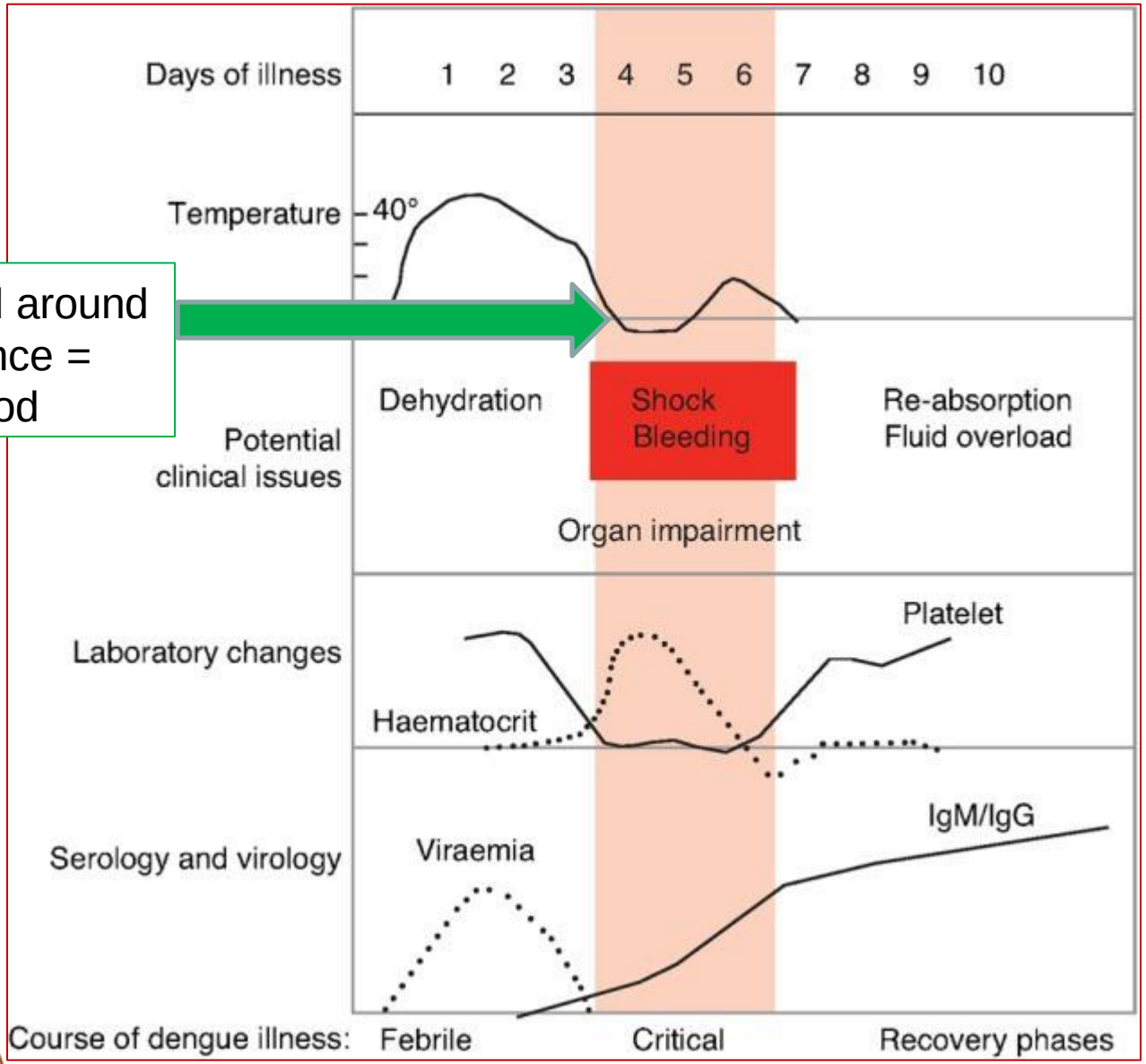
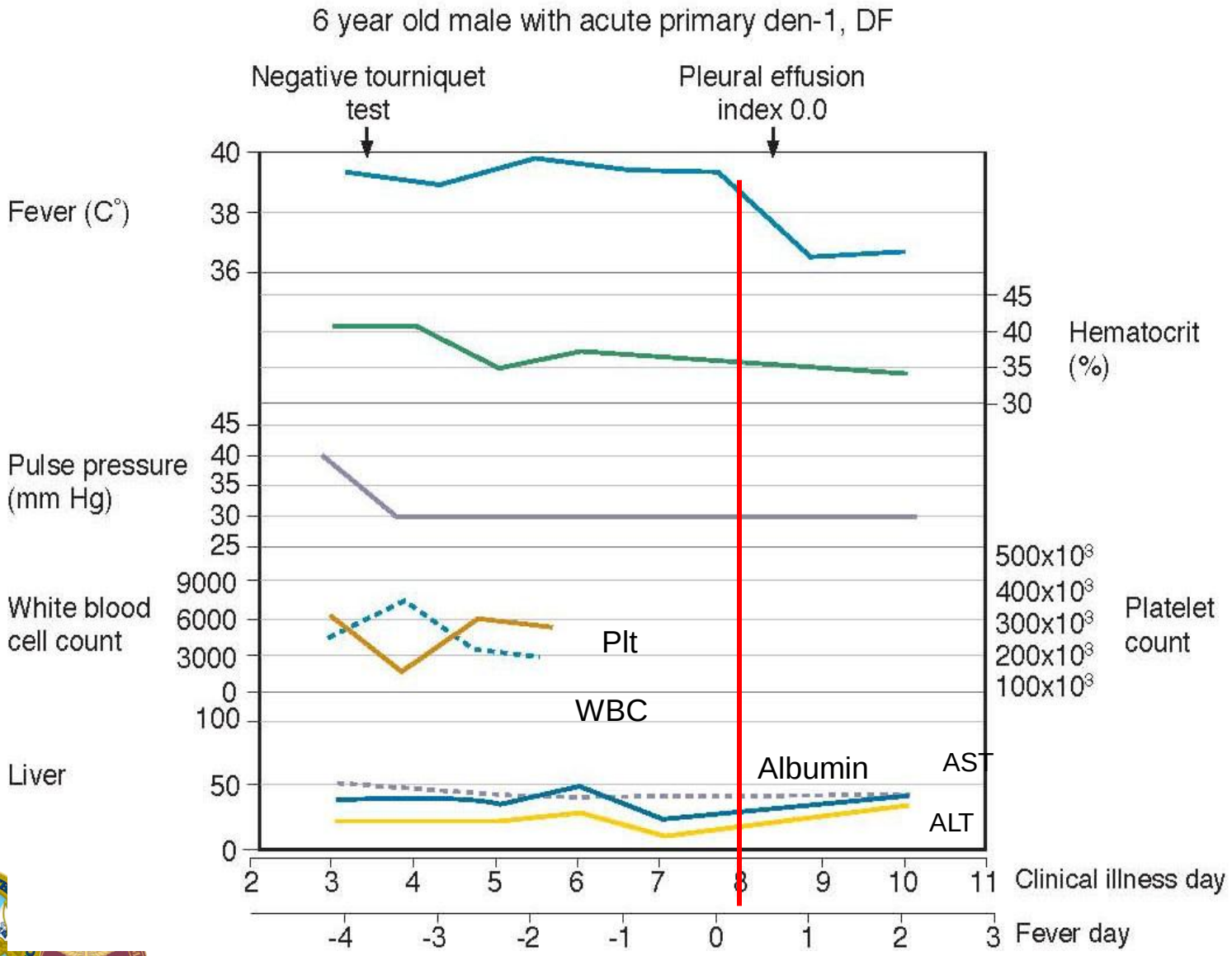

Endothelial cell dysfunction
Development of coagulation disorder
Endothelial cells: infection and replication in selective endotheliocytes
Liver: replication in hepatocytes and kupffer cells
Tissue macrophages
Bone marrow: replication in stromal cells
Apoptosis
Necrosis and/or apoptosis in liver and breach of its function
Apoptosis
Suppression of haemopoiesis
Release of toxic products into the blood
Soluble mediators: TNF-α, IFN-γ, IL-1, IL-2, IL-6, IL-8, IL-10, IL-13, IL-18, TGF-β, C3a, C4b, C5a, MCP-1, CCL2, VEGF, NO
Increase of coagulation
Imbalance profile of cytokine and other mediators
Activation of fibrinolytic system
Consumption of platelets

Dengue Clinical and Lab Parameters

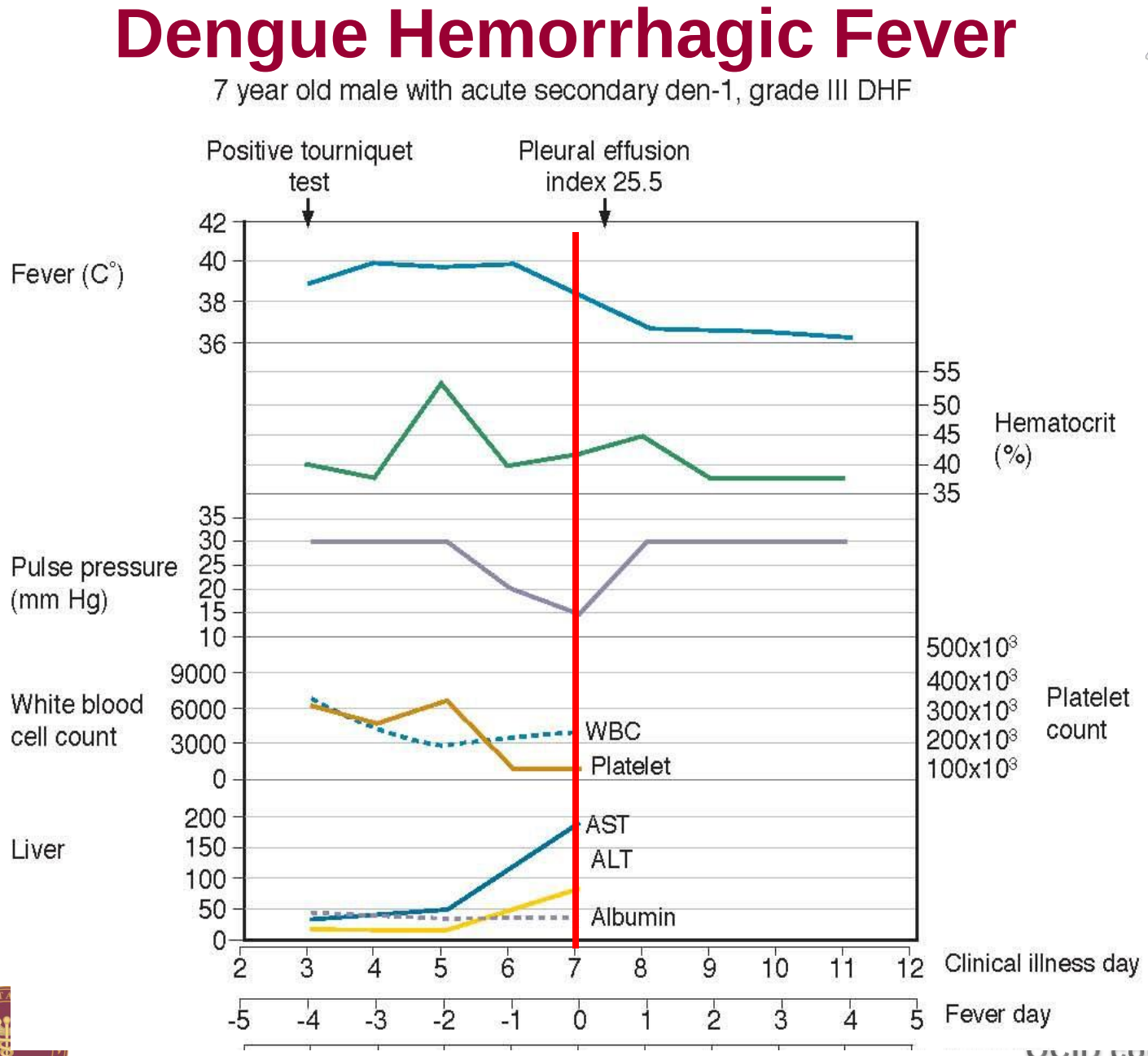
24 hr period around defervescence = danger period



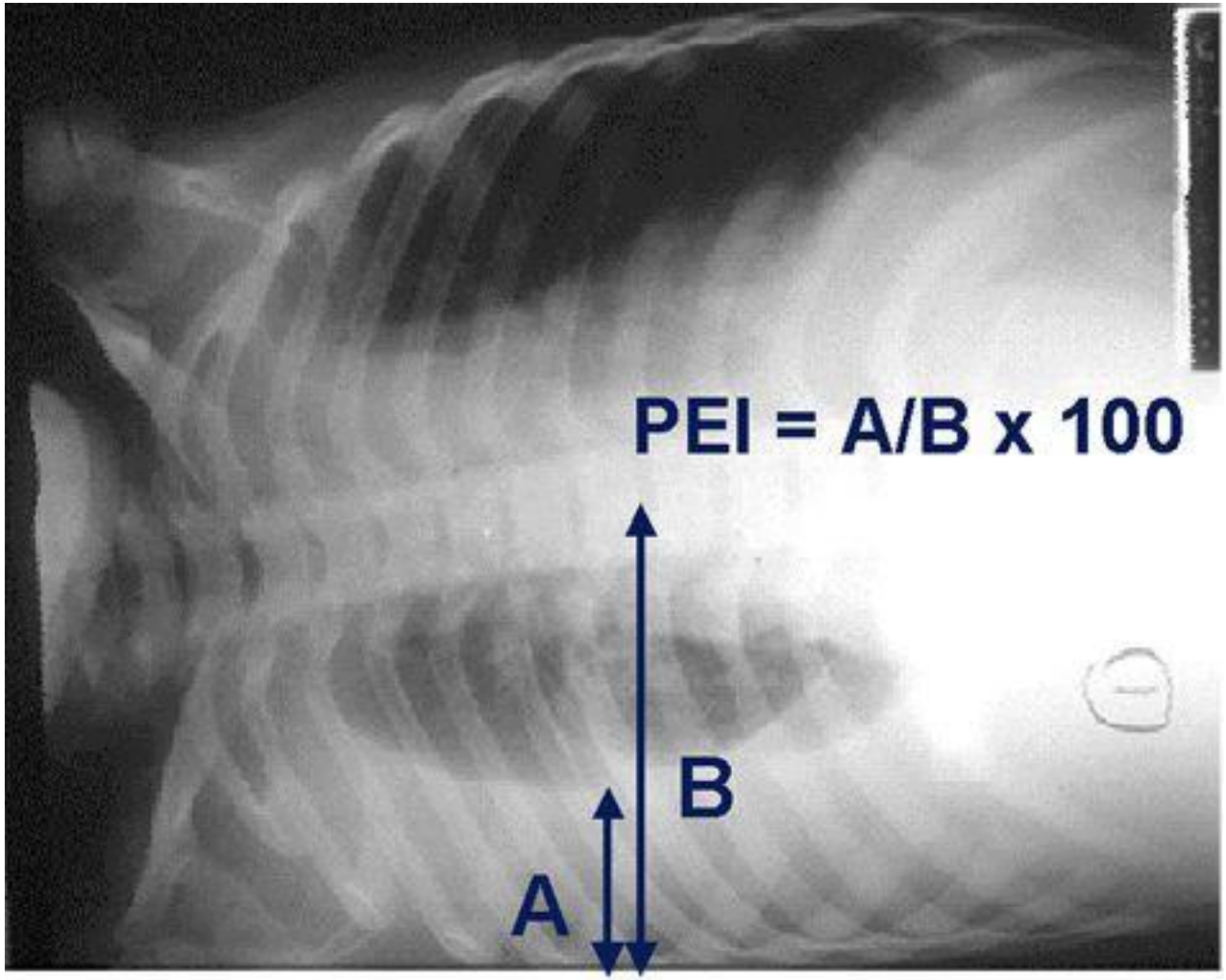
Dengue Fever



Dengue Hemorrhagic Fever

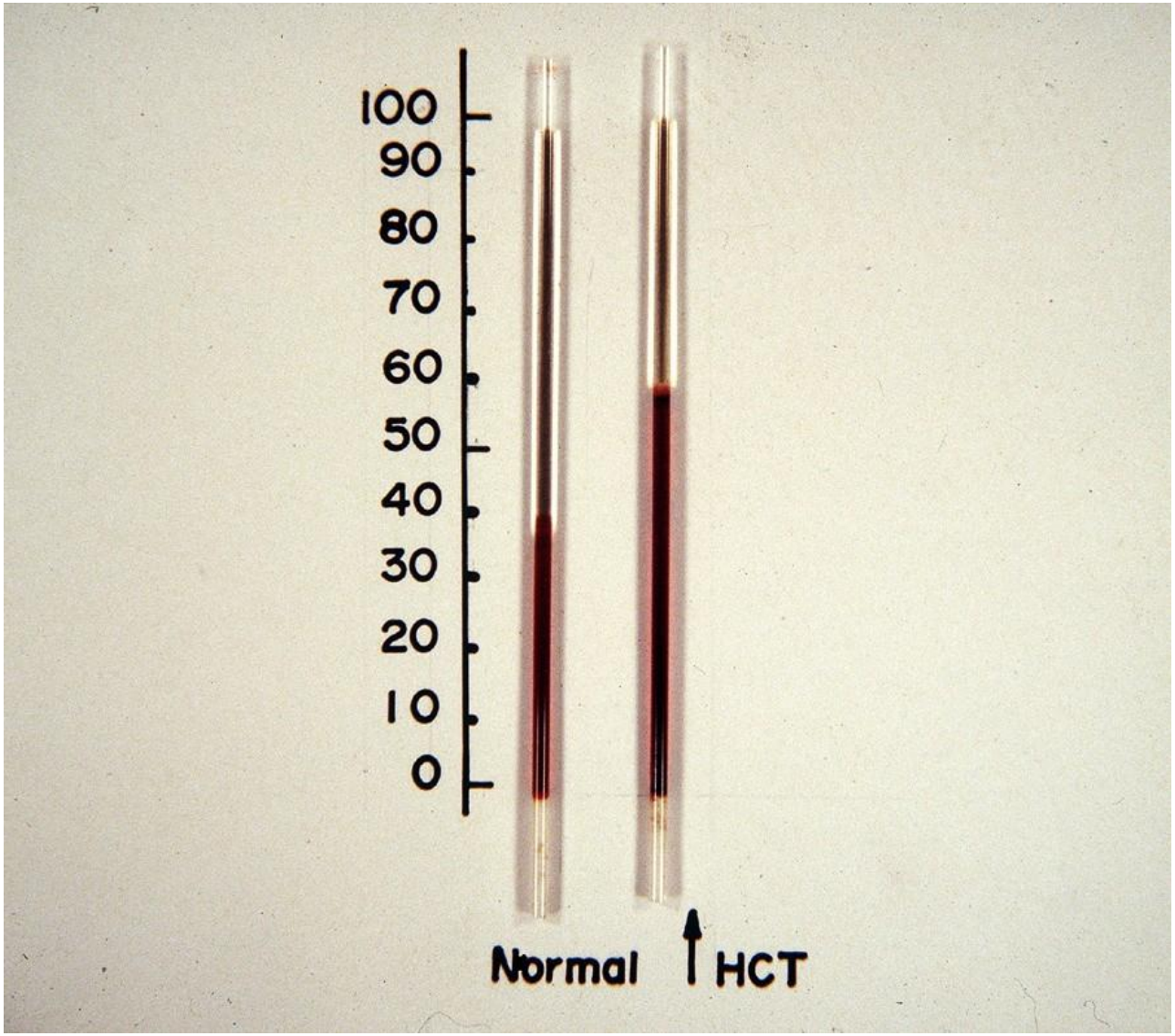


Pleural Effusion Index



R LAT decubitus X-ray showing a large pleural effusion, DHF the day after defervescence. Degree of plasma leakage may be quantified by means of the pleural effusion index. The pleural effusion index is calculated as 100 times the maximum width of the R pleural effusion, divided by the maximal width of the R hemithorax.

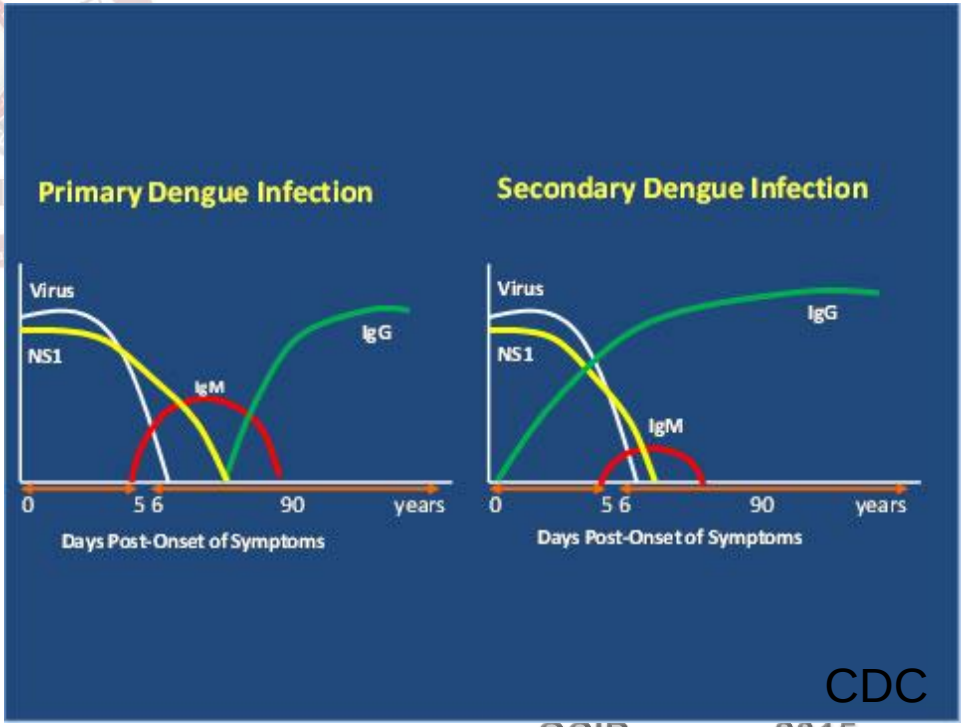
Hemoconcentration



Diagnosing Dengue

- FDA-cleared
  - **DENV 1-4 Real Time RT PCR (June 2012)**
  - **DENV Detect IgM Capture ELISA (April 2011)**

- RDT, Filter Paper Cards
  - No FDA-cleared RDT yet
    - FY17?
  - NS1 antigen detection
  - Antibody detection
    - IgM and IgG ELISA
    - Ideally combined with NS1 detection



CDC

Evaluation of diagnostic tests: dengue

Rosanna W. Peeling, Harvey Artsob, Jose Luis Pelegrino, Philippe Buchy, Mary J. Cardosa, Shamala Devi, Delia A. Enria, Jeremy Farrar, Duane J. Gubler, Maria G. Guzman, Scott B. Halstead, Elizabeth Hunsperger, Susie Kliks, Harold S. Margolis, Carl M. Nathanson, Vinh Chau Nguyen, Nidia Rizzo, Susana Vázquez and Sutee Yoksan

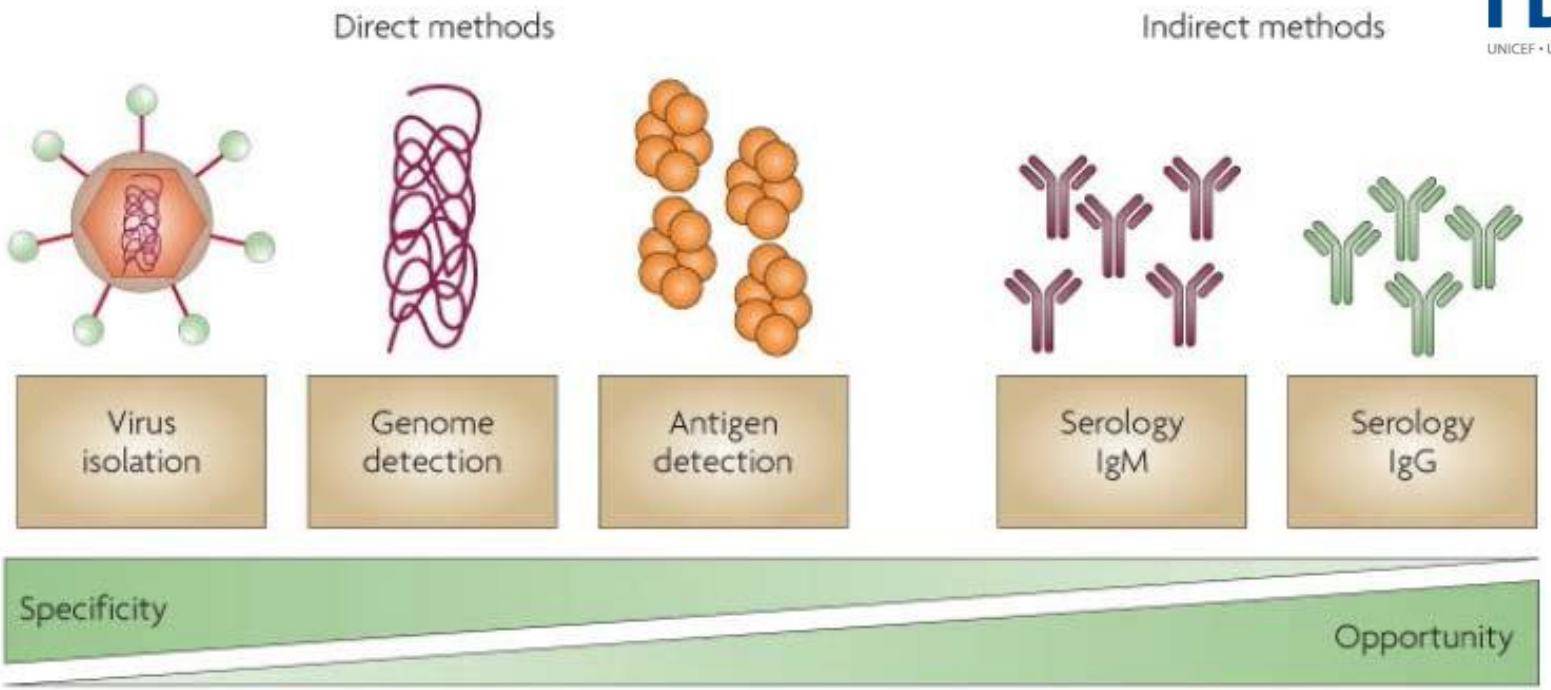


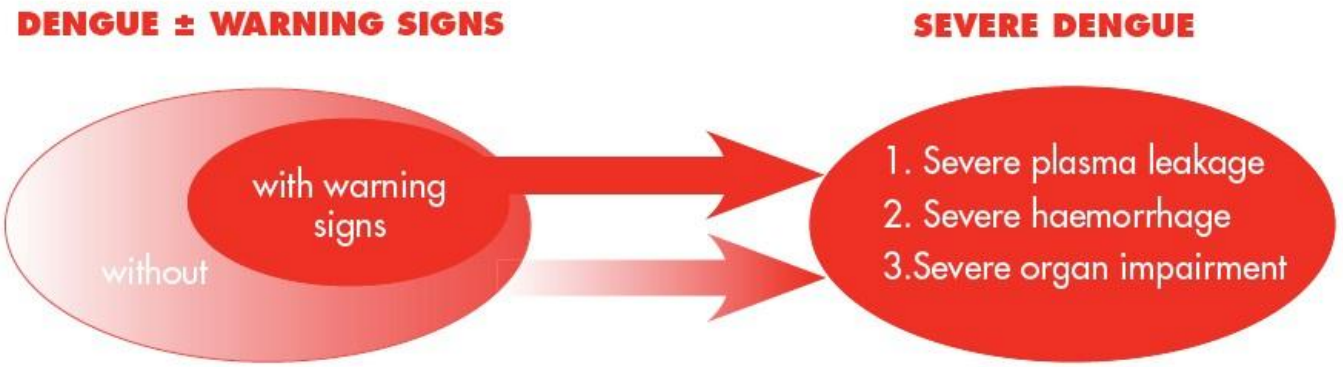
Figure 1 | **Comparative merits of direct and indirect laboratory methods for the diagnosis of dengue infections.** Opportunity refers to the fact that antibody testing is usually the most practical diagnostic option available.

Case Presentation

- 18 year old native from Thailand (moved to US at 10 years of age) presents in August with 2 days of illness including fever, headache, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. You decide to manage him as an outpatient. He fails to follow up as requested but does return day 6 of his illness afebrile with resolution of some symptoms but he now has abdominal pain, slight shortness of breath, and lethargy.

- What is the most reasonable management strategy at this point?
  - 1. Continue close follow up as outpatient, encourage PO fluid intake, this is the natural history of a resolving dengue infection
  - 2. Admit to the hospital, approach as a critically ill patient, this is a severe dengue virus infection
  - 3. Admit to the hospital, evaluate for another infectious disease process, these new symptoms represent a new medical problem
  - 4. Prescribe doxycycline, he probably has leptospirosis

Suggested Dengue Case Classification and Levels of Severity



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- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
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- Mucosal bleed
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- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

Dengue Treatment

DENGUE WITHOUT WARNING SIGNS

Group A
(May be sent home)

Group criteria

Patients who do not have warning signs
AND
who are able:

- to tolerate adequate volumes of oral fluids
- to pass urine at least once every 6 hours

Laboratory tests

- full blood count (FBC)
- haematocrit (HCT)

Treatment

Advice for:

- adequate bed rest
- adequate fluid intake
- Paracetamol, 4 gram maximum per day in adults and accordingly in children.

Patients with stable HCT can be sent home.

Monitoring

Daily review for disease progression:

- decreasing white blood cell count
- defervescence
- warning signs (until out of critical period).

Advice for immediate return to hospital if development of any warning signs, and

- written advice for management (e.g. home care card for dengue).

Dengue Treatment

DENGUE WITH WARNING SIGNS

Group B

(Referred for in-hospital care)

Group criteria

Patients with any of the following features:

- co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus, renal failure
- social circumstances such as living alone, living far from hospital

Laboratory tests

- full blood count (FBC)
- haematocrit (HCT)

Treatment

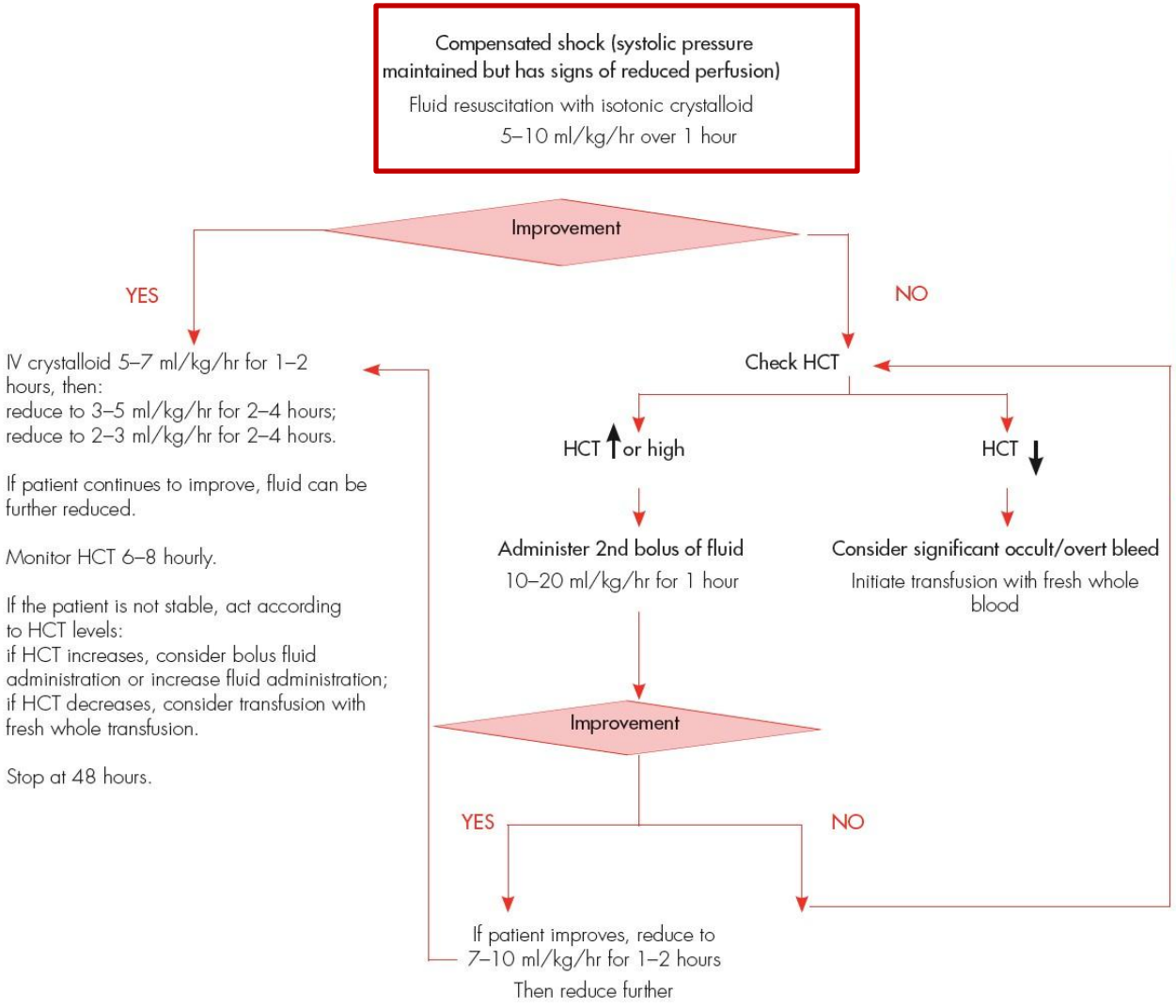
- Encouragement for oral fluids. If not tolerated, start intravenous fluid therapy 0,9% saline or Ringer's Lactate at maintenance rate.

Monitoring

Monitor:

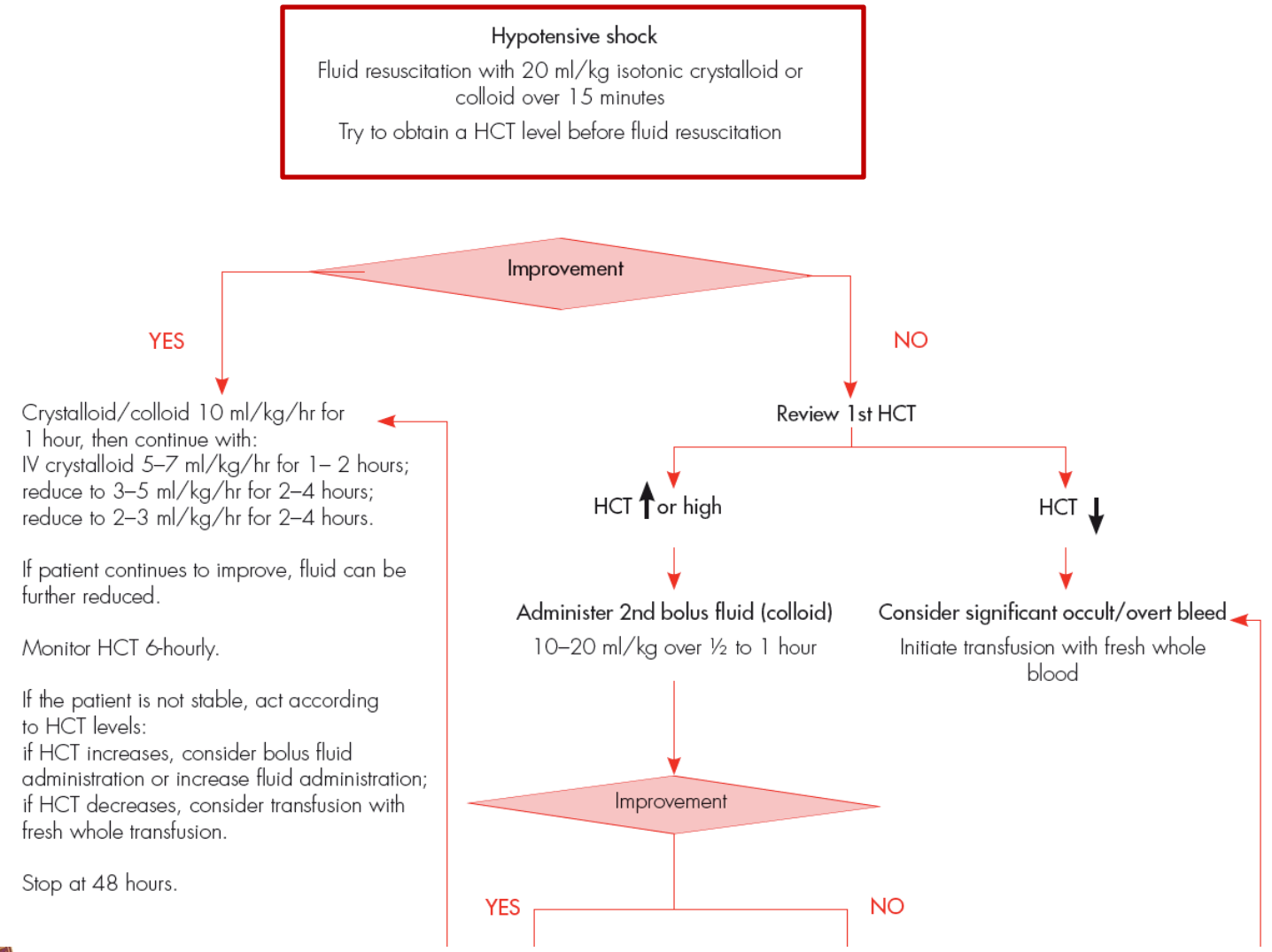
- temperature pattern
- volume of fluid intake and losses
- urine output (volume and frequency)
- warning signs
- HCT, white blood cell and platelet counts.

Algorithm for Fluid Management in Compensated Shock

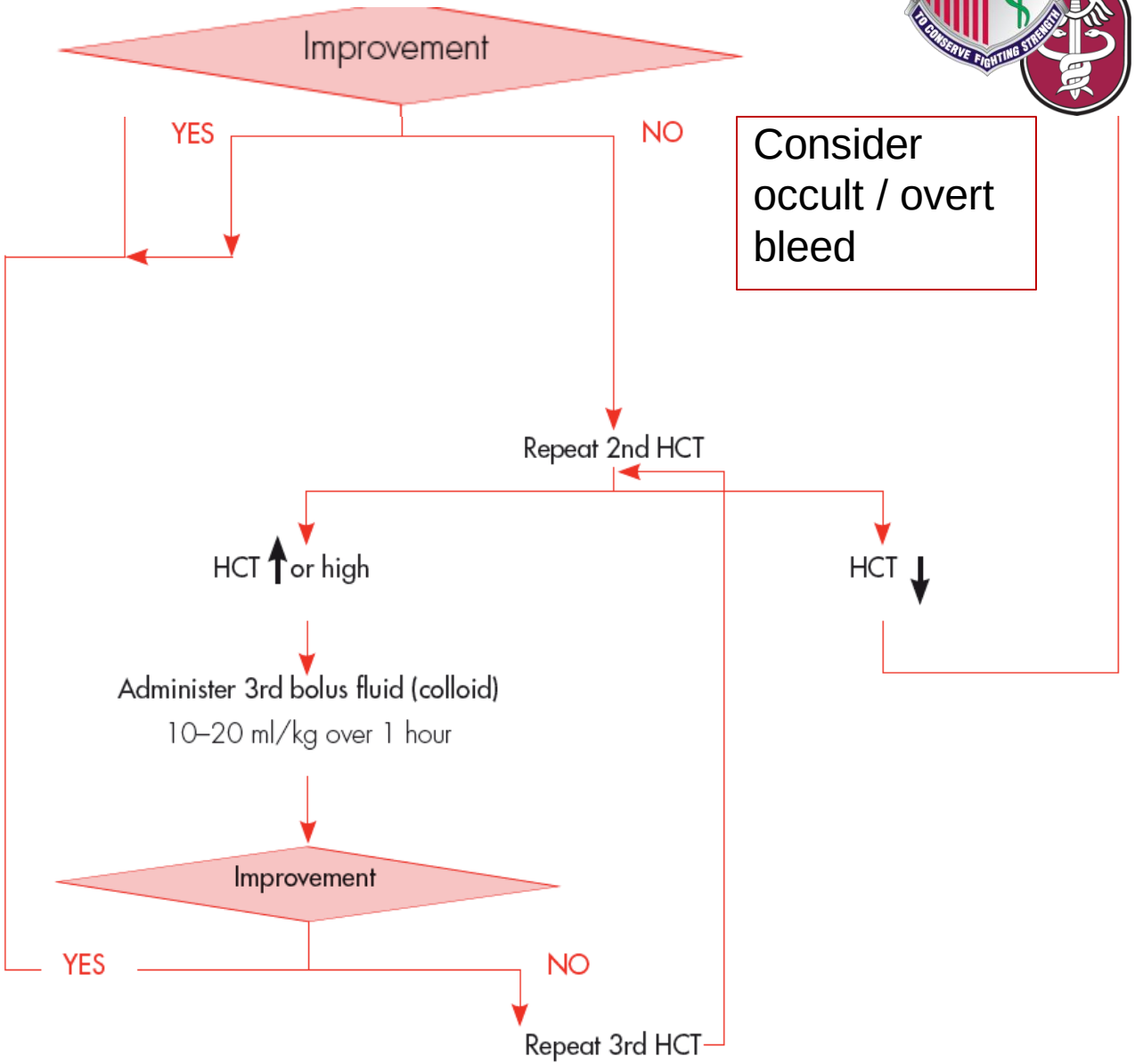


- Assess
- Intervene
- Re-assess

Algorithm for Fluid Management in Hypotensive Shock



- Assess
- Intervene
- Re-assess



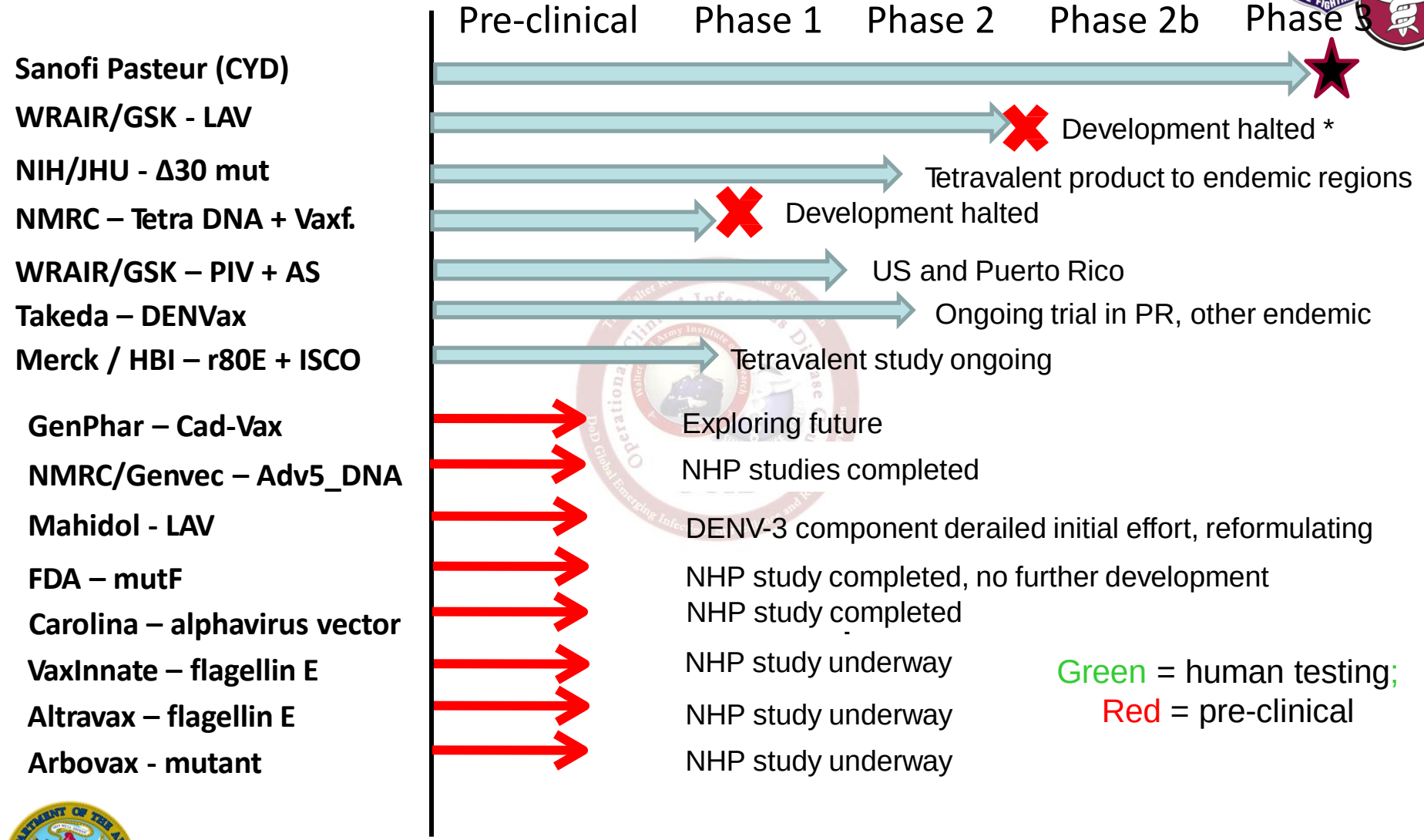
Consider occult / overt bleed

Textbox A. Good clinical practice and bad clinical practice

	Good practice	Bad practice
1	Assessment and follow-up of patients with non-severe dengue and careful instruction of warning signs to watch out for	Sending patients with non-severe dengue home with no follow-up and inadequate instructions
2	Administration of paracetamol for high fever if the patient is uncomfortable	Administration of acetylsalicylic acid (aspirin) or ibuprofen
3	Obtaining a haematocrit level before and after fluid boluses	Not knowing when haematocrit levels are taken with respect to fluid therapy
4	Clinical assessment of the haemodynamic status before and after each fluid bolus	No clinical assessment of patient with respect to fluid therapy
5	Interpretation of haematocrit levels in the context of fluid administered and haemodynamic assessment	Interpretation of haematocrit levels independent of clinical status
6	Administration of intravenous fluids for repeated vomiting or a high or rapidly rising haematocrit	Administration of intravenous fluids to any patient with non-severe dengue
7	Use of isotonic intravenous fluids for severe dengue	Use of hypotonic intravenous fluids for severe dengue
8	Giving intravenous fluid volume just sufficient to maintain effective circulation during the period of plasma leakage for severe dengue	Excessive or prolonged intravenous fluid administration for severe dengue
9	Avoiding intramuscular injections in dengue patients	Giving intramuscular injections to dengue patients
10	Intravenous fluid rate and frequency of monitoring and haematocrit measurement adjusted according to the patient's condition	Fixed intravenous fluid rate and unchanged frequency of monitoring and haematocrit measurement during entire hospitalization for severe dengue
11	Close monitoring of blood glucose, i.e. tight glycaemic control	Not monitoring blood glucose, unaware of the hyperglycaemic effect on osmotic diuresis and confounding hypovolaemia
12	Discontinuation or reducing fluid therapy once haemodynamic status stabilizes	Continuation and no review of intravenous fluid therapy once haemodynamic status stabilizes

Dengue Vaccine Development

Dengue Vaccine Pipeline 2013

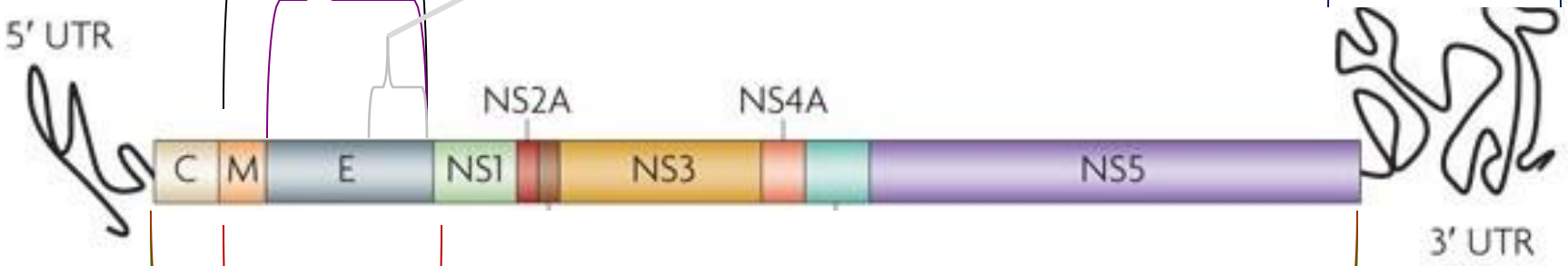


NMRC & others: DNA (preM+E) + adjuvant

Merck: 80% E recombinant
Expressed in Drosophila cells

NIH: Directed mutagenesis,
deletions, point mutations
Stand alone and chimeras

Various: Domain III antigen



WRAIR/GSK: PIV + adjuvant system
Full genome, inactivated, formalin

Sanofi P: YF 17D backbone
Dengue prM and E
Monovalents formulated as tetra-

Takeda: DENV-2 PDK backbone,
Directed mutagenesis, DENV-2/-1, -2/-3, -2/-4

Sanofi Pasteur's CYD Tetravalent Dengue Vaccine (TDV)

- Three doses at 0, 6, 12 months
- Completed two large phase 3 studies in Latin America and Asia among mostly seropositive children exposed to all 4 serotypes.
- Vaccine is efficacious against dengue fever
- Substantial protection against severe dengue
- Protection varied by serotype (DENV 2 worst)
- Lowest efficacy in 2-5 year olds
- Poor efficacy for subjects seronegative at baseline
- Marketing and licensure ?
- Fit for US travelers and military personnel ?

Development Challenges

- **Each DENV type may cause severe disease/death**
  - Viable vaccine requires efficacy against multiple types
  - Immune interference may prevent balanced response
- **Incomplete understanding of protection / pathology**
  - Will a poor dengue vaccine increase / worsen disease?
  - Extrapolating wild type infection data to immunization?
- **No validated immune correlate of protection**
  - No metrics or benchmarks for vaccine developers
  - Increases need for larger scale clinical trials

Development Challenges

- No validated animal model of disease
  - NHPs develop viremia and Nab but not disease
- No validated human infection model
  - Advancing vaccines based on Nab and NHP data
  - Efficacy trials may not capture efficacy vs. all DENVs
- Biologic assays used for endpoint determinations
  - Inter-assay variability notorious
  - Neutralizing antibody's ability to predict efficacy?
- Numerous indications with unique challenges
  - Needs vary at the time, space, and population level

Conclusions

- The world needs a dengue vaccine!
- Global dengue burden is increasing
- Maintain a high index of suspicion in febrile traveler
- High financial and societal cost associated with disease
- Numerous factors continue to drive transmission
- Numerous vaccine development challenges exist
- Dengue vaccine pipeline robust
- Numerous areas for expanded study exist

Questions?